A Dissertation on

STUDY OF THYROID FUNCTION ABNORMALITIES IN NEWLY DIAGNOSED HIV PATIENTS

Dissertation Submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032

In partial fulfilment of the regulations

For the award of the degree of

M.D. GENERAL MEDICINE

BRANCH-I

COIMBATORE MEDICAL COLLEGE

COIMBATORE

APRIL 2015

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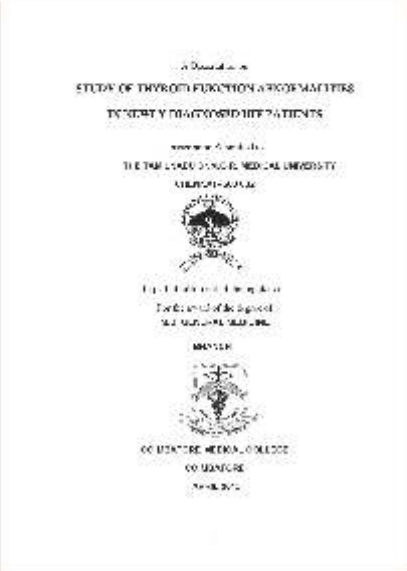

STUDY OF THYROID FUNCTION ABNORMALITIES


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I hereby declare that this dissertation entitled **"STUDY OF THYROID FUNCTION ABNORMALITIES IN NEWLY DIAGNOSED HIV PATIENTS"** is a bonafide and genuine research work carried out by me under the guidance of **Prof. M. RAVEENDRAN. MD.,** Department of medicine, Coimbatore medical college, Coimbatore.

Date:

Place: **Dr. DHANYA.S.KUMAR**

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LIST OF ABBREVIATIONS

AIDS	=	Acquired immunodeficiency syndrome
ART	=	Antiretroviral therapy
CD	=	Cluster differentiation
CDC	=	Centre for disease control
CMV	=	Cytomegalovirus
CI	=	Confidence interval
Cu.mm	=	Cubic millimetre
DNA	=	Deoxyribonucleic acid
ELISA	=	Enzyme linked immunosorbent assay
ESR	=	Erythrocyte sedimentation rate
T3-	=	triiodothyronine
FT3	=	Free triiodothyronine
T4	=	thyroxine
FT4	=	Free thyroxine

gp	=	glycoprotein
HAART	=	Highly active anti-retroviral therapy
Hb	=	Haemoglobin
HDL	=	High-density lipid
HIV	=	Human Immunodeficiency virus
I131	=	Radiolabelled iodine
microL	=	Microlitre
MNG-	=	multinodular goitre
NACO	=	National AIDS control organisation
nm	=	nano-metres
OI	=	Oppurtunistic infection
PAS	=	Periodic acid Schiff
RNA	=	Ribo-nucleic acid
T3	=	Triiodothyronine
T4	=	Thyroxine
TFT	=	Thyroid function test

TG	=	Thyroglobulin
TPO	=	Thyroid peroxidase
TRH	=	Thyrotropin releasing hormone
TSH	=	Thyroid stimulating hormone
WBC	=	White blood cells
WHO	=	World Health Organization

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ABSTRACT

BACKGROUND

There has been a significant increase in number of HIV patients in India. Endocrinal involvement is common in these patients especially involvement of thyroid in the form of subclinical hypothyroidism in various studies. There is little data on abnormalities of thyroid function tests in newly diagnosed HIV patients and only few studies undertaken in India and hence this study is done

OBJECTIVE

(1) To study thyroid function abnormalities in newly diagnosed HIV patients.

(2) To find out relation between thyroid function abnormalities and severity of illness in HIV infected patients.

METHODS: Fifty patients who are diagnosed to have HIV infection according to National AIDS Control Organisation (NACO) March 2007, who fulfill inclusion and exclusion criteria who attend Coimbatore medical college hospital from september 2013 to february 2014 were included with consent. Data was collected by using pre-tested proforma meeting the objectives of the study. All enrolled patients were investigated for total T3, total T4, TSH. It was compared with HIV status, CD4 count and WHO clinical stage of HIV disease

Of the 50 HIV patients, mean age was 38.84±8.34 years with 29 males. Of Thyroid dysfunction 60% were females. 62% -euthyroid, 38% -thyroid

dysfunction; of them 20 % had subclinical hypothyroidism, 12% - hypothyroidism, 2% - hyperthyroidism and 4%-sick euthyroidism. 57.89% of thyroid dysfunction patients had CD4 count <200 / μL p value 0.023 ODDS RATIO-.253 (CI-.075-.853). 46.67 % of WHO clinical stage 3 and 64.3 % of stage 4 patients had thyroid dysfunction and chi square value 10.025, p value 0.018. 57.89% of those with thyroid dysfunction had hemoglobin less than 9 g/dl p value- 0.003

CONCLUSION

There is significant association between age and thyroid dysfunction and gender had no statistical association with thyroid abnormalities in HIV patients. Subclinical hypothyroidism is the commonest thyroid dysfunction in newly diagnosed HIV. Thyroid dysfunction increases when CD4 count is <200/μL and WHO clinical stages 3 or 4. Hemoglobin <9 g/dl and pallor is associated with thyroid dysfunction. Hence thyroid function screening may be done in newly diagnosed HIV patients with – CD4 <200/ μL or WHO clinical stage 3 or 4 or if patient has hemoglobin <9 g/dl or pallor. This screening helps in early recognition of thyroid abnormalities before antiretroviral therapy initiation as these drugs themselves induce thyroid dysfunction.

Key words – HIV, thyroid dyfunction, subclinical hypothyroidism, CD4, WHO clinical stage, hemoglobin.

INTRODUCTION

The AIDS- Acquired immunodeficiency syndrome was first reported in 1981.The etiologic virus Human immunodeficiency virus was discovered in 1983. For the discovery of the virus Luc Montagnier and Francoise Barre-Sinoussi were bestowed with nobel prize in 2008. [1]

HIV has become a pandemic with global statistics showing 35.3 million people living with HIV in 2012 and World wide around 2.3 million people have become newly infected with HIV and around 1.6 million people died from AIDS and its complications . From the beginning of the AIDS epidemic an estimated 36 million people have died of AIDS.

In India around 1.16 lakhs new HIV infections were reported in 2011 and estimated number of people living with HIV is 20.9 lakhs as per 2011 statistics. Wider access to Antiretroviral therapy has caused a decrease in estimated annual deaths due to AIDS by 29% in 2011 as compared to 2007 numbers.[3]

HIV infection affects almost every organ of the body including the endocrine system. Adrenal gland is most often involved but clinical adrenal dysfunction is not usually seen. Thyroid disorder is also common in HIV infection. Though clinical manifestation is not common thyroid hormone level alteration is common in HIV infections and has been found in many previous studies.

Thyroid function alteration is present in 10 – 15 % of patients with HIV infection. Both hypothyroidism and hyperthyroidism may be seen. Most common is subclinical hypothyroidism. In the HAART era around 10 % patients are noted to have elevated TSH levels. This may be due to immune reconstitution [5] . In advanced HIV disease , infection of thyroid gland due to opportunistic pathogen like pneumocystis jeroveci, CMV, mycobacteria, toxoplasma or Cryptococcus may cause thyroid dysfunction.Thyroid dysfunction has been in many studies correlated with advancement of infection and lowered CD 4 cell count. There are not many Indian studies to establish these relations, and so this study is undertaken. The thyroid function abnormalities in patients who are not already exposed to antiretroviral therapy brings out the effect of the HIV infection alone on thyroid glandular function. To include patients with all grades of advanced HIV infection at different severity and different CD4 count range we have included newly diagnosed HIV patients in our study, as, if not done so , patients with lower CD4 counts and those who are eligible for ART by clinical severity of disease would already have been started on ART as per NACO guidelines. To avoid the effect of drugs on thyroid profile we selected newly diagnosed HIV patients and there thyroid profile was correlated with their clinical stage of HIV disease and CD4 counts.

AIMS AND OBJECTIVES OF THE STUDY

(1) To study thyroid function abnormalities pattern in newly diagnosed HIV patients at varying severity of illness at diagnosis

(2) To find out relation between thyroid function abnormalities and severity of HIV illness – immunological severity as assessed by CD4 count and clinical severity as assessed by WHO clinical stage of the illness

REVIEW OF LITERATURE

Acquired Immunodeficiency syndrome is a secondary immunodeficiency condition which is caused due to infection by Human Immunodeficiency virus. In 1981 AIDS was first reported as an emerging fatal infectious disease. HIV is a retrovirus causing profound immunosuppression. This immunosuppression makes the infected person more susceptible to many unusual infectious organisms leading to opportunistic infections. This makes those infected vulnerable to many secondary neoplasms and autoimmune and endocrine and neurologic manifestations and thus is a multisystem disorder. It is the sudden increased prevalence of rare infections Pneumocystis carinii pneuomonia and kaposi's sarcoma in young homosexual adults and injection drug abusers in 1981 that a suspicion towards the emergence of a new immunodeficiency disorder with new unrecognized pathogen arose. In 1983 the causative agent was identified from a patient with lymph node enlargement and by 1984 it was established beyond doubt that HIV was the etiologic agent responsible for AIDS. Enzyme Linked Immunosorbent assay a sensitive test for HIV was then developed by the year next.

The pattern of AIDS case reports suggested that this disease agent could be transmitted through sexual contact (homosexual and

heterosexual), sharing of drug injecting needles or Infected blood product transfusion, and vertically from mother to child.

INDIAN SCENARIO [1]

First case of HIV in India was reported in 1986. It was reported first in female sex workers in Chennai, Tamil Nadu. HIV epidemic in India is of Type IV pattern. In this kind of pattern new infections occur initially in high risk persons - female sex workers and injection drug abusers and after this it spreads to the so called Bridge Population that is the clients of FSW and sexual partners of drug users and then ultimately infects the general population.

Young adults (15-49 years) account for 89% of the burden of HIV infection. The male to female ratio is 3:2 . India has a 'concentrated epidemic', the prevalence being significantly higher among various high-risk groups (MSM, IDU, FSW and STD clinic attendees) than among antenatal subjects .

HIV -VIROLOGY

Human Immunodeficiency virus is a lentivirus, a member of retrovirus subfamily. HIV is cytopathic and cytotoxic and high levels of viral gene expression causes death of the infected cell and sometimes even the adjascent cells [4].

STRUCTURE OF HIV

HIV has an icosahedral structure .It is an enveloped virus .The diameter of HIV is 120 nm[6] . It also has a lipid bilayer with around 72 spikes of glycoprotein . The different types of glycoprotein are

- gp 120
- gp41 for HIV- 1
- gp 36 for HIV – 2.

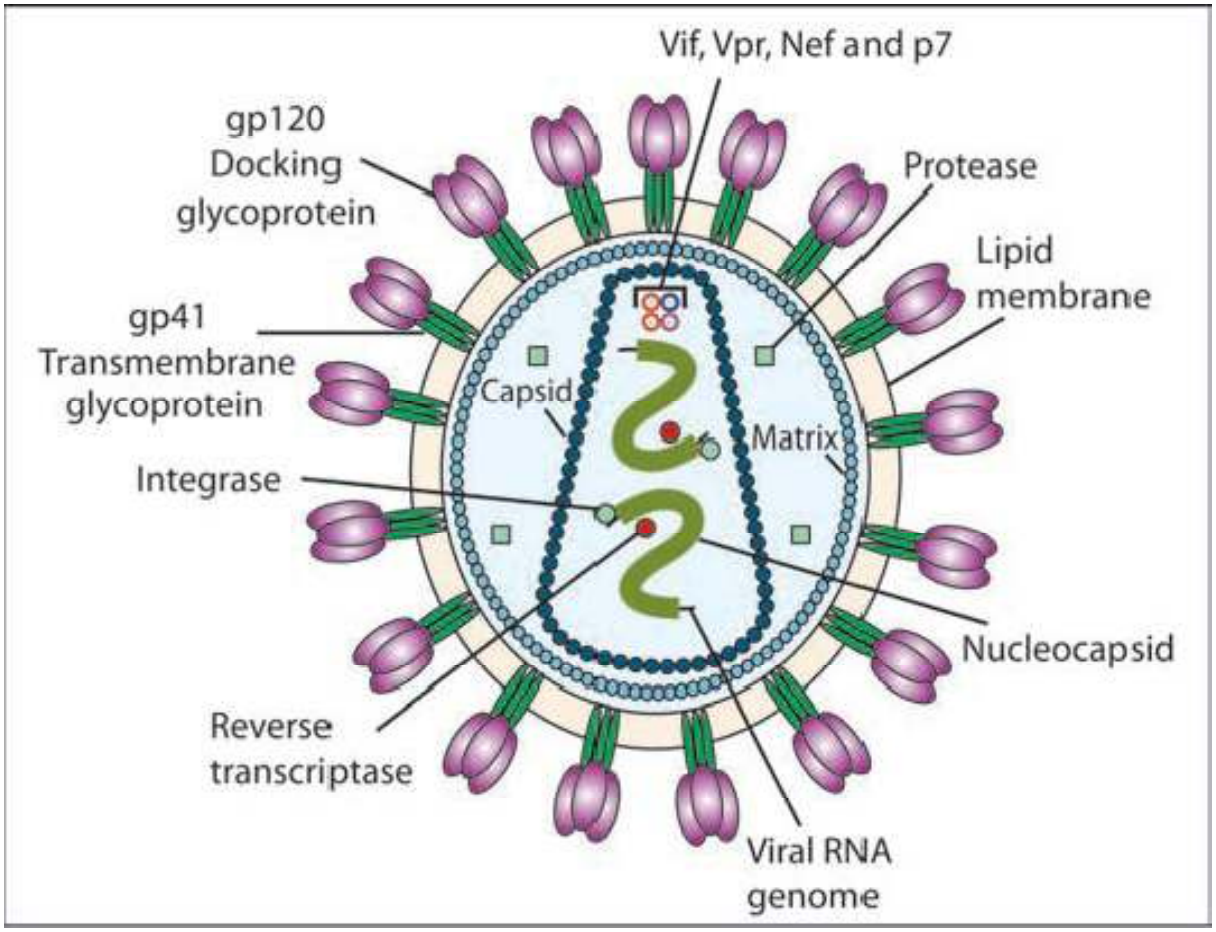

Figure 1: HIV Morphology

The gp 120 provide binding site for the cellular receptors. The virion has 2 RNA molecules within the protein capsid p24. Within the capsid are viral RNA dependent DNA polymerase Pol that is reverse transcriptase enzyme.The capsid (p24) is surrounded by a matrix layer (p17) that is enclosed by lipid bilayer.[5]

HIV genome

The genome of HIV contains 3 structural genes - gag ,pol , env.[5]

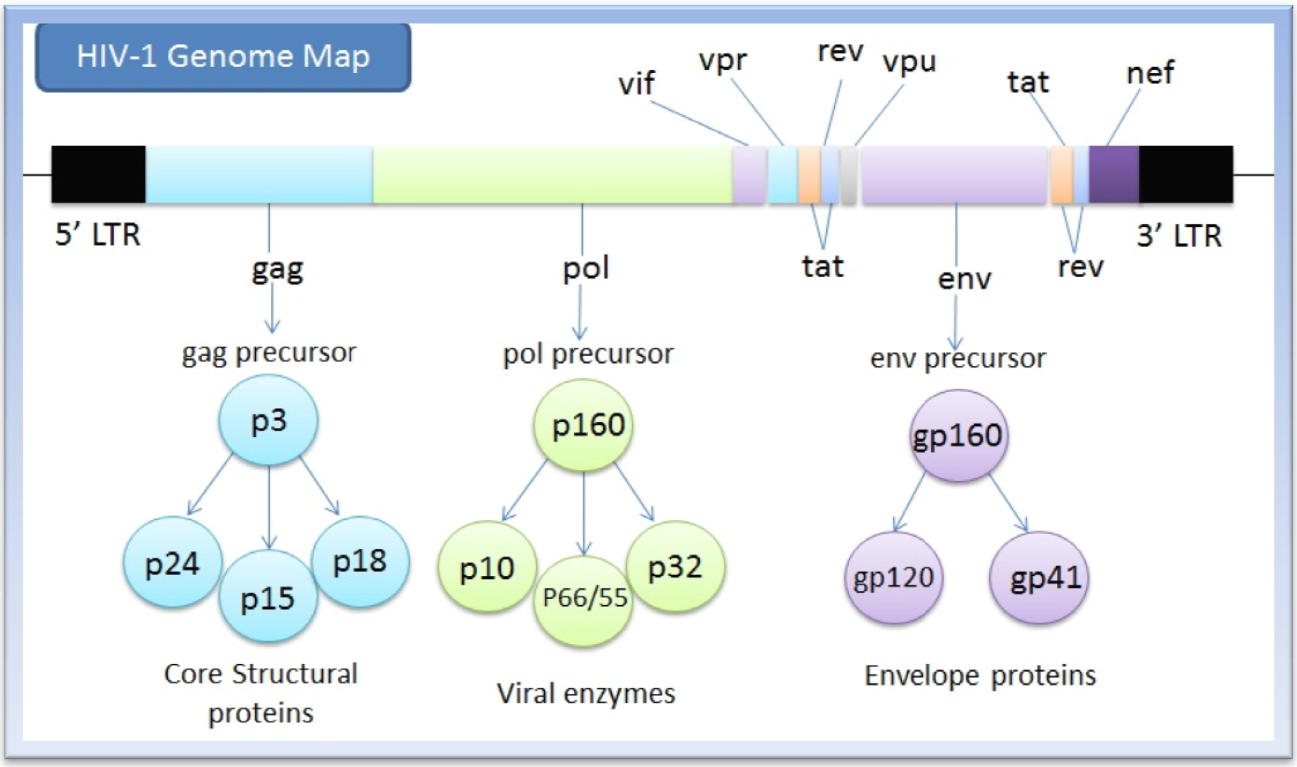

Figure 2 . HIV – 1 genome

In India the most common mode of transmission is heterosexual the statistics in India for mode of transmission is shown in the following figure

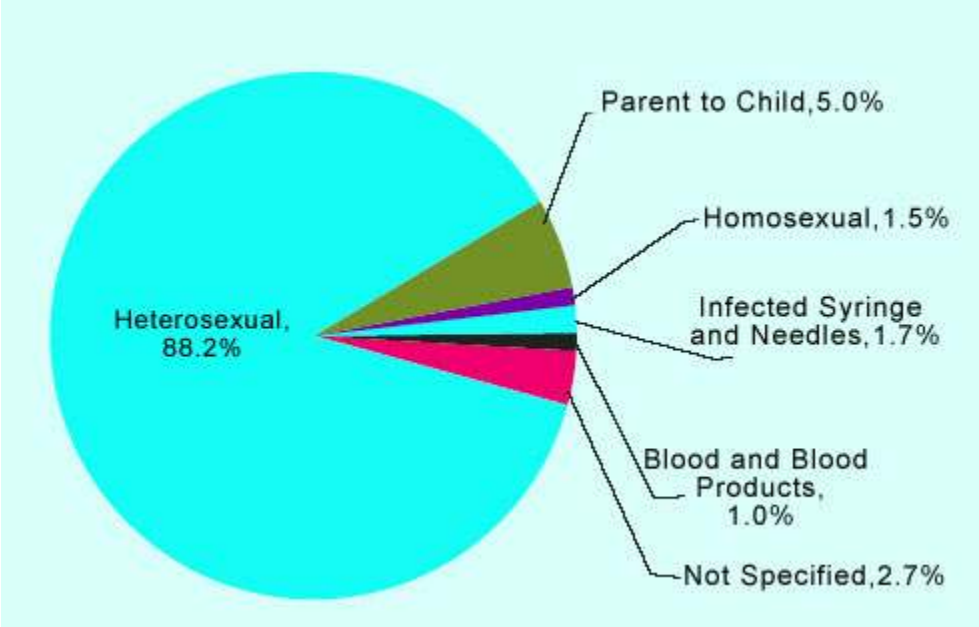

Figure 3 . Modes of HIV transmission in India

The risk of transmission is

- highest when blood or blood products are the source of infection that is more than 90% to 95 %[12]
- 15-40% for vertical transmission that is mother to child transmission
- 0.5-1% for intravenous and injectable drug users
- 0.2- 0.5 % via genital mucosal membrane

HIV REPLICATION

- gp 120 protein binds to the CD4 molecule which is the gp 120 receptor[13]
- This requires a co-receptor called CCR5 which helps the CD4 molecule for fusion and entry of the HIV 1 .
- Fusion of the virion with the host membrane occurs via gp 41
- HIV - RNA is uncoated and it is internalized to the target cell.
- The enzyme called reverse transcriptase of the virion causes the reverse transcription of the virion RNA into ds DNA .
- DNA translocates to nucleus and with the help of integrase , the DNA integrates with host chromosome
- When cellular activation occurs this leads to transcription of the proviral DNA to mRNA and also to the virion genomic RNA
- Then transcribed mRNA is translated to proteins
- Posttranscriptional modification occurs
- The HIV proteins enzyme and also the genomic RNA assemble to form the core of the virion.
- It then acquires plasma membrane of the host cell and buds off

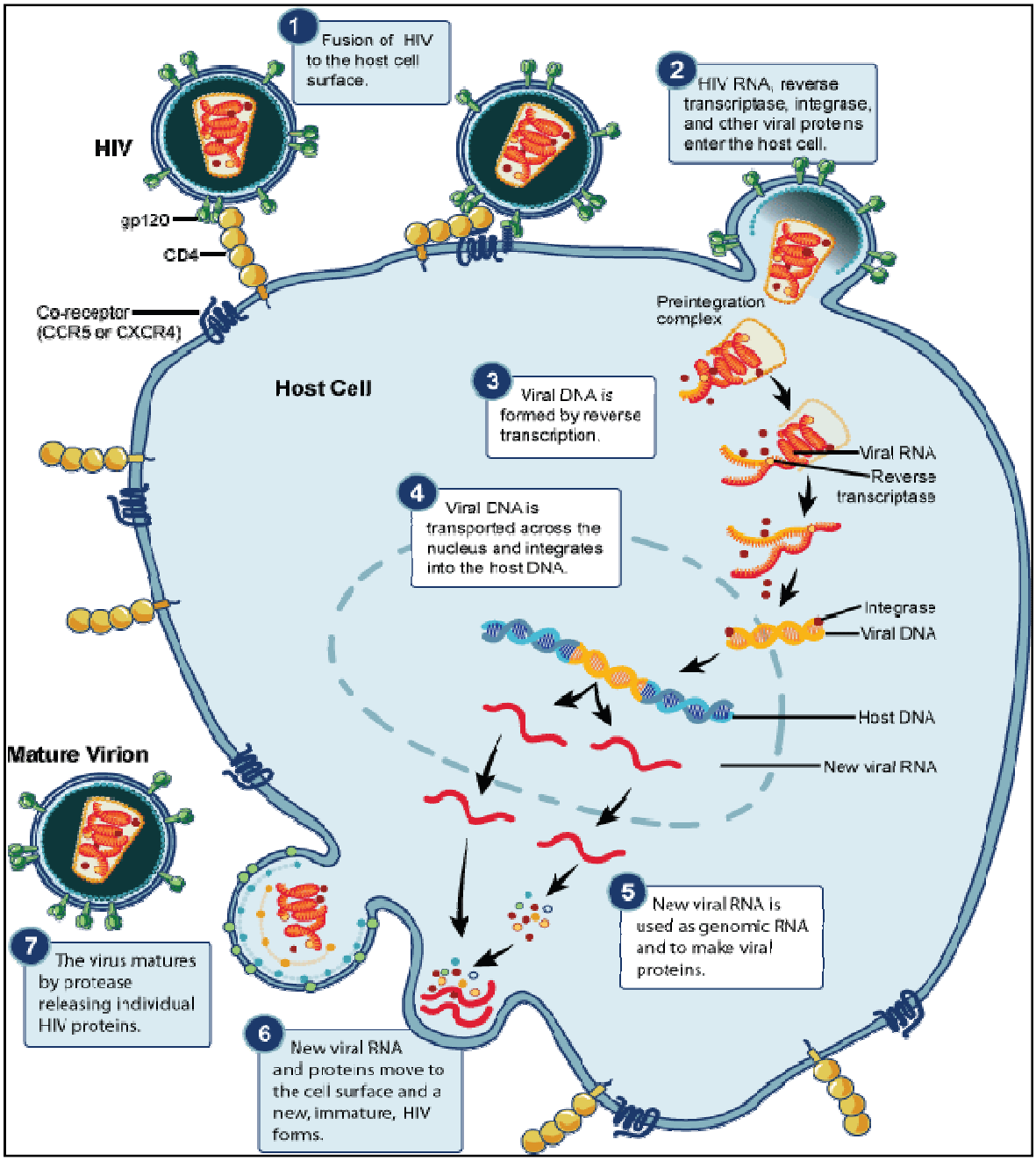

Figure 4 . HIV Replication cycle

PATHOGENESIS

PRIMARY INFECTION :

- When there is infection by human immunodeficiency virus 1 initially in the acute stage there is viral replication in CD 4 + T lymphocytes. CD 4 + T cells in the GALT and MALT express HIV co-receptor CCR5 and hence are susceptible to HIV-1 infection. This infection leads to viral replication which in turn causes high HIV RNA titres . It reaches higher to about Ten lakh copies per millilitre within a fornight. Due to this high HIV load patients have a syndrome known as Acute Retroviral Syndrome.

- Following this fall in the peripheral CD4+ T lymphocyte cell counts occurs in the primary infection which causes opportunistic infections. In few weeks time the CD8 + T lymphocyte begin to form in response to HIV and causes control of multiplication of the virus.

- This leads to decrease in the load of HIV which leads to a state called as the SET POINT.

- The rate of progression of HIV to full blown AIDS is determined by the load of the virus at the SET POINT .

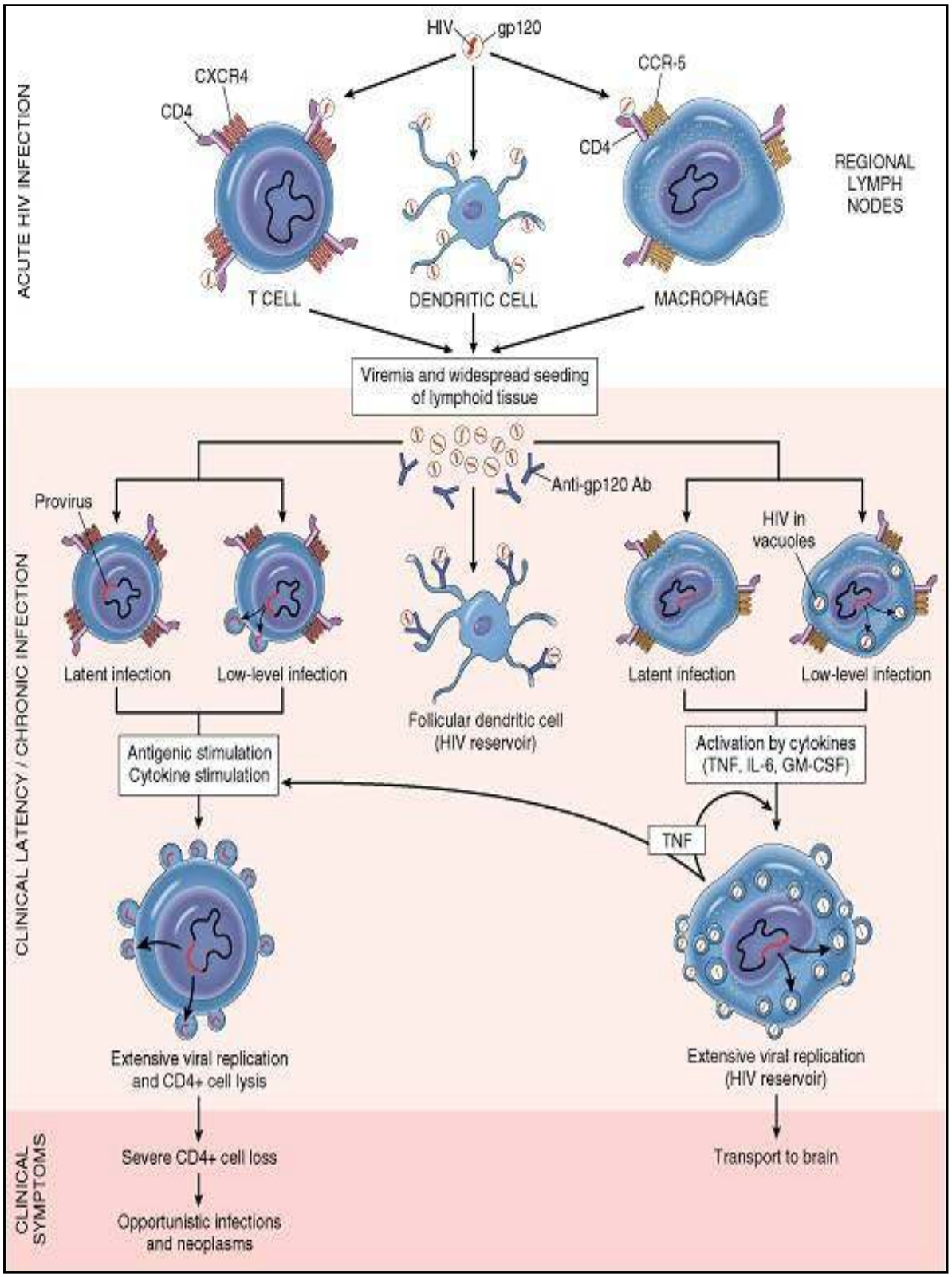

Figure 5. HIV Pathogenesis

IMMUNITY THAT IS SPECIFIC TO HIV

- HIV activates dendritic cell through TLR
- This causes production of interferon IFN 1
- This interferon stimulates immunity against HIV 1
- Interferon 1 also activates CD4+ and CD 8+ cells
- Natural killer cells - activated when cell is infected with HIV
- NK cell activation leads to prevention of progression of illness in the long run may be by decreasing HIV multiplication.
- Humoral immune activation has a latency , it is not reached till about maximum load of the virus is reached . this latency is called the window period
- Window period is the period in which there is viremia but the antibodies cannot be detected in blood.
- The antibodies that develop act by preventing the gp 120 from reacting with CD4 and other coreceptor.

- The depletion of CD 4 is very selective. This is responsible for the impaired adaptive immune response in human immunodeficiency virus.

- CD8+T lymphocytes control the human immunodeficiency virus infection by causing direct cytolysis of the cell which is infected by the virus.

- CD 8 + T cells also secrete soluble factors called macrophage inflammatory protein one beta which binds to chemokine receptor and thus prevents the entry of human immunodeficiency virus into the cell.

- Complete sterilizing immunity which is specific to HIV cannot be achieved by the CD8+ lymphocytes, because of the latent infection which remains within the CD4 + cells memory cells that are formed soon after the infection.

- These latent cell are not recognized by the CD 8 + T cells because the quiescent cells are not able to synthesise HIV proteins .

- The HIV enzyme reverse transcriptase has got only low fidelity and this leads to mutations with each replication cycle.

THE EFFECT OF HIV-1 REPLICATION ON THE IMMUNE SYSTEM

There is immune system activation chronically due to continuous viral multiplication. This kind of chronically active immune mechanism can cause non - specific inflammatory activation and this leads to translocation of the microbes due to decrease in CD4+ T lymphocytes in GALT. It is the chronic activation of immune system which leads to the fall in the CD 4 + T lymphocytes.

The markers of immune system activation on the CD 4+ T lymphocytes and the CD 8 + T lymphocytes better correlates with rate at which the CD 4 falls than does the quanitity of the load of the virus in patients who are not treated. There are activation markers detected increasingly on the

- ✓ NK cells
- ✓ B cells
- ✓ CD 4 + lymphocytes
- ✓ CD8 + T lymphocytes

This activation of markers is associated with rise in the rate of turnover of the cells. NK cells don't function effectively causing ineffective control over other viral infections

B cell function is also impaired causing hyper-gammaglobulinemia and accelerated generation of auto-antibodies. When vaccinated the response by production of antibody is impaired when CD4+ falls.

Cells which are most productively infected cells remain alive only for shortened time that is approximately 1 day before dying due to the cytopathic action of virus and cytolytic T cells of the host or NK cells. CD 4 cells which are lost thus lead to CD 4 depletion . The immune system which is chronically activated causes the non infected CD 4 + cell death and this is the main mechanism of the fall in CD 4 count. The qualitative memory response against recall antigen falls earlier that is even before CD4 count decreases to less than 200 cells per microlitre. Its also found that the CD4 and CD8 cells undergo immune exhaustion and hence the immune response mediated by CD 8 cells against the viruses like CMV and EBV is qualitatively poor. This is due to anergy and also depletion of the CD 4 + T cells which are inevitable for the sustained CD 8 + lymphocyte response.

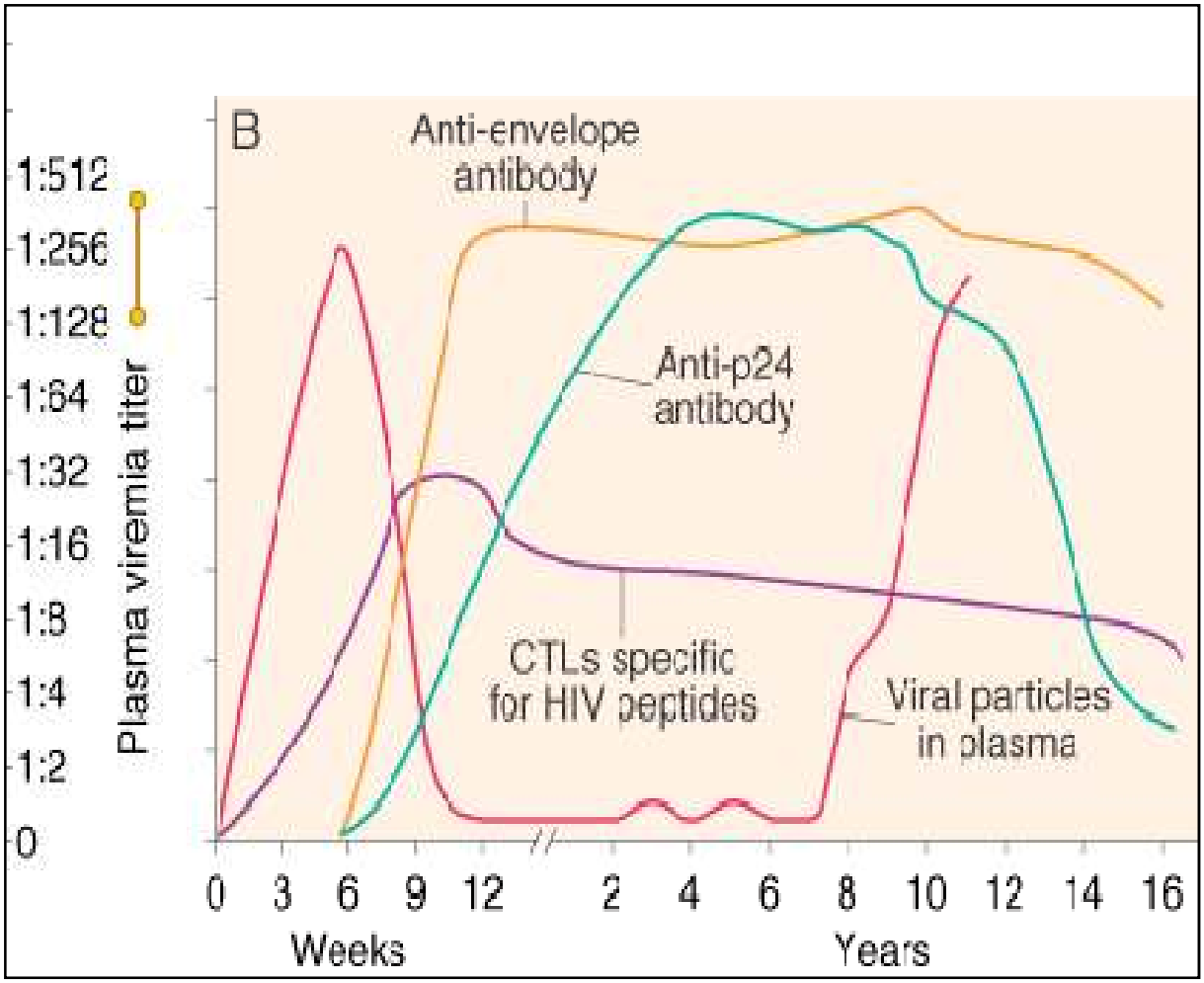

Figure 6 . Immune Response to HIV Infection

Autoimmune Phenomena

- The autoimmune phenomena in HIV-infection is due to chronic immune system activation as well as molecular mimicry by viral components.
- Autoimmunity usually occur in the absence of autoimmune disease, a number of clinical manifestations due to autoimmunity are described.

- Autoimmune phenomena include antibodies to lymphocytes, to platelets or to neutrophils. Antiplatelet antibodies thus may cause thrombocytopenia of HIV disease.

- Antibodies to nuclear and cytoplasmic components of cells and antibodies to cardiolipin; CD4 molecules; CD43 molecules; C1q-A; variable regions of the T cell receptor ; Fas; denatured collagen; and IL-2. In addition, autoantibodies to serum proteins, including albumin, immunoglobulin, and **thyroglobulin,** have been reported.

- There is antigenic cross-reactivity between HIV viral proteins (gp120 and gp41) and MHC class II determinants, and anti-MHC class II antibodies reported in HIV infection.

- These antibodies could potentially lead to the elimination of MHC class II–bearing cells via antibody-dependent cellular cytotoxicity (ADCC), although this has not been clearly demonstrated to occur . In addition, regions of homology exist between HIV envelope glycoproteins and IL-2 as well as MHC class I molecules.

- The occurrence and/or exacerbation of psoriasis, idiopathic thrombocytopenic purpura, Graves' disease, antiphospholipid antibody syndrome, and primary biliary cirrhosis in HIV are thus seen.

- With the effective antiretroviral therapy, an immune reconstitution inflammatory syndrome (IRIS) has become common. IRIS is an autoimmune-like phenomenon characterized by a paradoxical deterioration of clinical condition, which is usually compartmentalized to a particular organ system, in individuals in whome cART has recently been initiated. It is associated with a decrease in viral load and at least partial recovery of immune competence, causing rise in CD4 count .

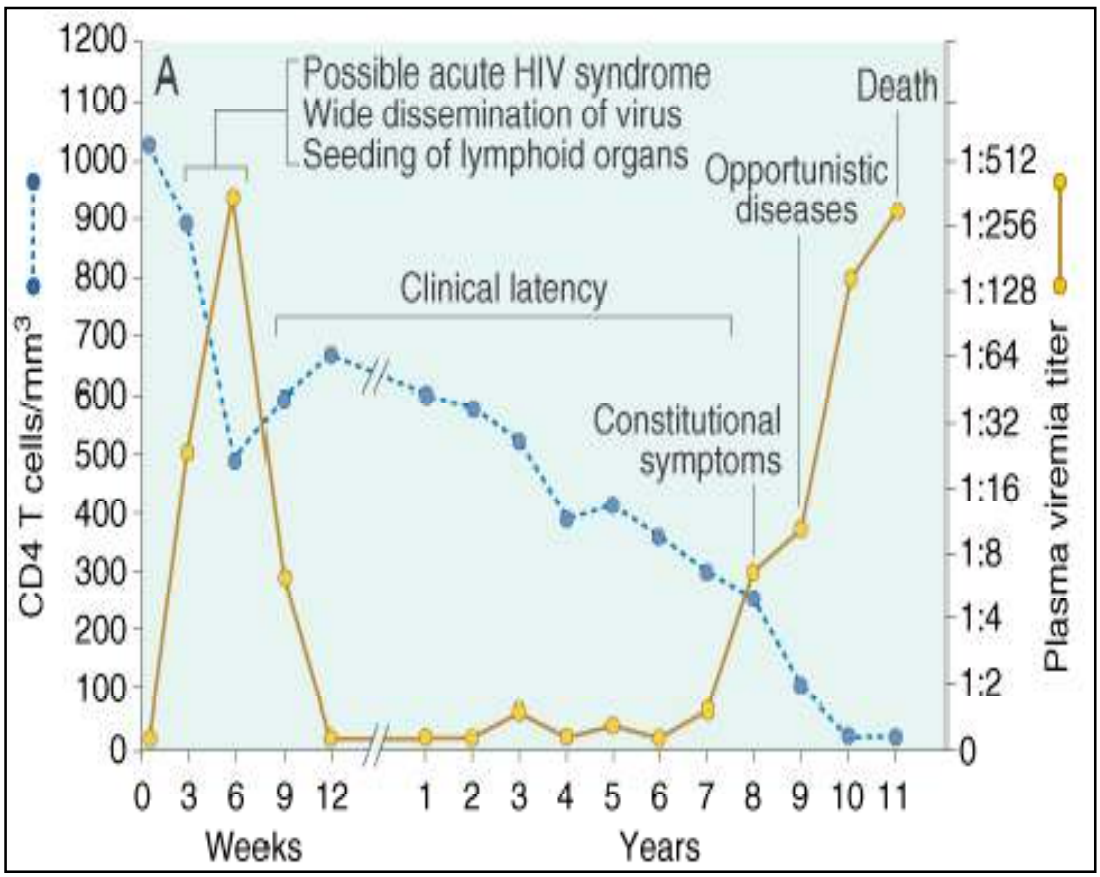

Figure 7. Course of HIV Infection

Clinical Features of AIDS

It can be of mild disease to severe. They range from a mild acute illness to severe disease. Symptoms range from fever with weight loss or diarrhea or generalized lymph node enlargement or opportunistic infections or neurological diseases and also secondary neoplasm. The typical infectious diseases and neoplasms in HIV and AIDS is detailed in the clinical stages of infections. Opportunistic infections are the most common cause of mortality in AIDS patients. The prevalence of infections can be reduced by the treatment with HAART.

NACO GUIDELINES [7]

In India the Case Definition for AIDS

Case definition for AIDS in India , was revised in October, 1999 by the national AIDS control organisation

Case Definition of AIDS in persons > 12 years

1. Two positive tests for HIV infection by ELISA/ RAPID / SIMPLE test

AND

2. Any one of the following criteria:-

a) *Significant weight loss* (> 10% of body weight) within last one month

Chronic diarrheoa and prolonged fever

b) Tuberculosis: may be Extensive pulmonary or disseminated, or miliary, or extrapulmonary tuberculosis.

c) Neurological impairment is present that is preventing independent activities of daily living, not known to be caused by conditions that are unrelated to HIV

d) esophageal candidiasis

e) Clinically life -threatening / recurrent episodes of pneumonitis

f) Kaposi's Sarcoma

g) Other conditions:-

Cryptococcal meninigitis

Neurological Toxoplasmosis

Cytomegalovirus retinitis

Recurrent H. zoster or herpes infection involving multiple dermatomes

Disseminated molluscum

DIAGNOSIS OF HIV

The diagnosis of HIV infection is by one of the following

- The demonstration of antibodies against HIV
- The direct detection of HIV or one of its components. [10]

Antibodies to HIV generally appear in the circulation 2 to 12 weeks after infection. The standard screening test for HIV infection is the ELISA- Enzyme linked immunosorbent assay. This solid phase assay considered as a screening test with a sensitivity of >99.5%**.**[6]

The western blot test is a highly specific test; it detects specific antibody to viral core protein (p24) and envelop glycoprotein gp41.[8]

Quantitative nucleic acid testing. :

- Polymerase chain reaction (PCR)
- the branched DNA (b-DNA)
- the nucleic acid sequence-based amplification (NASBA)
- ligase chain reaction (LCR)
- quantitative detection of reverse transcriptase activity.

"Viral load" testing can be used as a prognostic and as a therapeutic marker.[9]

I. The screening tests

1) ELISA test for different viral antigens

2) Rapid tests

a) Dot blot assay

b) Particle agglutination

c) HIV spot and coombs test

d) Flowmetric microparticulate technologies

The sensitivity of the ELISA is > 99.5%, the specificity of positive results by two different techniques approaches to 100% even in low risk population.[10] Factors associated with false positive tests are autoantibodies, hepatic disease, recent influenza vaccination and acute viral infection.

II. The confirmatory tests are:

1) Western blot

2) Immunoblot

3) Line immuno assay

4) ELISA with different antigen system or with different principle of test which makes the test more specific

5) Indirect fluorescent antibody test (IFA)

6) Radio immune precipitation test (RIPA)

7) Polymerase Chain reaction (PCR) for HIV RNA

The confirmatory test commonly used is the western blot test. Its specificity when combined with ELISA is >99.99%. The indeterminate results occur with early HIV infection, HIV-2 infection, autoimmune diseases, pregnancy and recent tetanus toxoid injection.[10] But as the test is cumbersome and also costly the practice now is to perform two different types of ELISA or an ELISA with any of the rapid tests. A serum positive in both tests is considered positive. This is used in the diagnosis of HIV infection by NACO guidelines.

Revised World Health Organization clinical staging of HIV/AIDS for adults and adolescents (2005) [75]

World Health Organization developed the clinical staging and immunological classification of HIV and related illness to help those countries out where inadequate resource makes lab measurements of CD 4 counts and HIV viral load in plasma not feasible. The WHO clinical stage can be used to determine the eligibility of the patient for antiretroviral treatment. Medical decision for HIV patients is made entirely based on the clinical features. This staging system is a practical and also accurate way to manage HIV patients with many international studies showing agreement between the clinical features in staging system and CD 4 count.

Table 1: WHO CLINICAL STAGES OF HIV/AIDS

WHO CLINICAL STAGE	DISEASE
WHO Clinical Stage I	Asymptomatic
	Persistent generalized lymphadenopathy
WHO CLINICAL STAGE	**DISEASE**
WHO Clinical stage II	unexplained weight loss <10%
	Recurrent bacterial URI
	Angular chelitis
	Recurrent oral ulcer
	Seborrheic dermatitis
	Onychomycosis

Table 1: WHO CLINICAL STAGE of HIV / AIDS

WHO CLINICAL STAGE III	weight loss greater than 10 percent not otherwise explained
	Unexplained chronic diarrhea
	Persistent fever which is unexplained
	Persistent oral candidiasis
	Oral hairy leukoplakia
	Pulmonary TB
	Severe bacterial infections
	Nectrotizing stomatitis or gingivitis
	Anemia which is not explainable Hb < 8 or neutrophil count less than 500 or platelet count less than 50000 per microlitre

WHO CLINICAL STAGE IV	Extrapulmonary TB
	PCP pneumonia
	Recurrent severe bacterial pneumonia
	Central nervous system toxoplasmosis
	HIV encephalopathy
	HIV wasting syndrome
	Cryptococcosis
	Progressive multifocal leukoencephalopathy
	Esophageal candidiasis
	CMV infection
	Lymphoma
	Kaposi sarcoma
	HIV Associated Nephropathy
	HIV associated Cardiomyopathy
	Invasive carcinoma cervix
	Visceral leishmaniasis

HIV A MULTISYSTEM DISEASE

Respiratory System

Infectious pulmonary process[15] : Mycobacteria tuberculosis

pneumococcal pneumonia with sepsis

Haemophilus influenza pneumonia

Pseudomonas aeruginosa

Pneumocystis jerovecii pneumonia

Non infectious pulmonary disease: Kaposi's sarcoma

Non Hodgkin's lymphoma

Interstitial pneumonitis

Sinusitis : Bacterial sinusitis

Fungal sinusitis

Pneumocystis jerovecii : most common opportunistic infection in the HIV infected patients which has typical radiological features like the Chest X ray showing the perihilar or diffuse infiltrates

Central Nervous System [15]

- Toxoplasmosis – most common space occupying lesion in patients with HIV
- CNS lymphoma – Non Hodgkin's lymphoma
- AIDS dementia complex – most common cause of altered sensorium in HIV patients.
- Cryptococcal meningitis
- HIV myelopathy : spastic paraparesis and sensory ataxia
- Progressive multifocal leukoencephalopaty : viral infection – JC virus which destroys myelin by infecting the oligodendrocytes .It usually Presents with aphasia, limb apraxia , ataxia, hemiparesis, cortical blindness, focal signs related to occipital lobe.

Peripheral Nervous System Diseases

- Sensory neuropathy , Mononeuropathy
- Inflammatory demyelinating polyneuropathy
- Transverse Myelitis

Myopathy

Proximal muscle myopathy

Zidovudine can also induce myopathy

Retinitis

CMV retinitis –fluffy opacities / exudates

perivascular Hemorrheage

Oral Lesions

- Oral candidiasis
- Hairy leukoplakia
- Angular cheilitis
- Aphthous ulcers
- Gingival disease

Gastro intestinal involvebilaiment

- Candidial oesophagitis
- Heptatic involvement : HIV causes chronic active hepatitis
    - Hepatitis C virus infections

- Hepatitis B virus hepatitis
- Cytomegalovirus infection of the liver
- Mycobacterial disease of the liver
- Lymphoma involving the liver

- Biliary disease : these diseases are induced by Cytomegalovirus , cryptosporidia and microsporidia

  Acalculous cholecystitis , Sclerosing cholangitis , Papillary stenosis

- Enterocolitis :

  Bacterial : campylobacter , Salmonella , Shigella

  Virus : Cytomegalovirus , Adenovirus

  Protozoans : entamoeba, Giardia etc

  HIV itself can cause the enterocolitis known as AIDS enteropathy

  HIV gastropathy and malabsorption – HIV infected patients secrete less acid they become prone to many infections like salmonella and campylobacter.

Skin Manifestations[16]

Herpes simplex infection is common and often more severe in AIDS patients .Herpes zoster is also common in HIV disease

Molluscum contagiosum : spread widely over the patients skin

Staphylococcus: most common bacterial skin disease. Presents as folliculitis , superficial abscess, bullous impetigo. It can progress to sepsis

Bacillary angiomatosis : Bartonella mimic lesions of kaposi's sarcoma

Fungal infections : dermatophytes and candida

Seborrhoeic dermatitis caused by Malasezzia furfur

Xerosis : severe pruritis in HIV patients with no rash

Psoriasis can be very severe in patients who are HIV seropositive

HIV Related Malignancies[15]

AIDS defining malignancies are

1.Kaposi's sarcoma , 2.Non Hodgkins lymphoma, 3.primary lymphoma of the central nervous system and 4. invasive cervical carcinoma

Endocrine manifestations in HIV infection

Adrenal Insufficiency: deficiency of the glucocorticoid and or the mineralocorticoids secreted by the adrenal gland. In HIV patients at

autopsy there is found to be high incidence of adrenal involvement.[17,19] CMV infection of adrenal gland is found.[18] But clinically and biochemically, adrenal insufficiency is uncommon. The trio of hyperkalemia hyponatremia and hypotension in HIV patients is not always adrenal insufficiency, it can occur due to many causes in advanced HIV disease. Drugs like ketoconazole used to treat fungal infection in HIV patients causes inhibition of adrenal corticosteroid synthesis[20] and it also causes blunting of the cortisol response when ACTH is given[21]. Rifampicin alters the metabolism of the glucocorticoids causing increased excretion of the steroids making increased glucocorticoid replacement to achieve therapeutic levels.[22]

HYPOGONADISM

The clinical features are fatigue, loss of energy, depressed mood and loss of libido and poor self esteem[23]. Frank hypogonadism is not seen instead borderline low testosterone level is found in HIV patients which has functional importance and need be treated with Androgen replacement at moderate doses. Hypogonadism should be thought of in HIV infected patients with weight loss or infection or symptoms specific of hypogonadism like altered growth of hair and beard and sexual dysfunction or testicular atrophy[24]. Estimation of Total serum level of testosterone is to be done. Normal value is around 200 to 250 ng/d to

1000 to 1100 ng/dl . Those found to have <450 to 500 ng/dl need to be treated. Serum estradiol level is used in women to assess for hypogonadism. The therapy is testosterone intramuscular injection every one to three weeks so that approximately 100mg/week is provided. Oxandrolone an oral androgen is now approved for use in AIDS-associated weight loss and the dose used is 20 mg.[27]

PITUITARY DYSFUNCTION

There are reports of Toxoplasma gondii infiltrating the pituitary[28] in advanced stages of HIV disease. Inadequate ACTH response to adrenal insufficiency and hypogonadotropic hypogonadism. Elevated levels of prolactin is also reported in advanced HIV disease. Posterior pituitary dysfunction can present as hyponatremia.[29] Hyponatremia is due to stress or drug induced SIADH [32]. Another differential diagnosis is renal salt wasting syndrome.[30] Isolated hyponatremia is commonly seen in HIV disease in advanced stage of illness and it had a poor prognosis.[31]

PANCREATIC DYSFUNCTION

This causes hypoglycemia if hyperinsulinemia occurs and diabetes if hypoinsulinemia occurs. Pentamidine [33] which was used to treat pneumocystis pneumonia caused pancreatic endocrine disturbance which caused hypoglycemia. Pentamidine is a strong beta cell toxin. Rapid

destruction of beta cell causes rapid release of large quantity of insulin leading to hypoglycemia.[34] The drug remains in the system for weeks due to long half life hence hypoglycemia may be persistent for days to weeks. Later on patient can go in for diabetes mellitus with or without ketoacidosis.[35]

THYROID GLAND FUNCTION

Abnormal thyroid function pattern called the sick euthyroid syndrome is found in advanced HIV disease. Other than this subclinical hypothyroidism and hypothyroid patterns are also seen in HIV patients at various stages of illness[38]. There are some reports of pneumocystosis[39] of thyroid gland and involvement of thyroid gland by cytomegalovirus[40] and also Kaposi sarcoma.[41]

THYROID OVERVIEW

Normal thyroid gland is made up of two lobes joined by the isthmus. It is 0.5 cm thick, 2cm wide, and 2cm in height. It lies anterior to trachea that is it lies between the cricoid and the suprasternal notch.

PHYSIOLOGY OF THYROID HORMONE[42]

Iodine absorbed in the gut and is converted to iodide and is transferred into the thyroid cell by "iodide trapping". The trapped iodine is oxidised to iodine and combines with tyrosine to form monoiodotyrosine (MIT) and Diodotyrosine (DIT). The MIT and DIT are coupled to form T3, where as two DIT couple to form T4. Oxidation, Iodination and coupling reactions are catalyzed by the enzyme Thyroid Peroxidase. Thyroid hormones are then bound with thyroglobulin till secretion. T4 is secreted from the thyroid gland in about twentyfold excess over T3. Both thyroxin and the T3 are bound to plasma proteins, including thyroxine binding globulin (TBG), 25 trans- thyretin and also albumin. The concentration of TBG is relatively low (1–2 mg/dL), but because of its high affinity for the thyroid hormones , it carries about 80% of the hormones that are bound. Albumin has comparatively low affinity for thyroid hormones but has high plasma concentration (3.5 g/dl) , that it binds around 10% of the T4 and 30% of T3. TTR carries

about 10% of T4 but little T3. In the periphery T4 is converted to T3 by the deiodinase enzymes. Type I deiodinase, which is located primarily in thyroid, liver, and kidneys, has a relatively low afinity for T4. Type II deiodinase that has a higher affinity for T4 and is found primarily in the pituitary gland, brain, brown fat, and thyroid gland. Expression of type I deiodinase allows it to regulate T3 concentrations , this is important in levothyroxine (T4) replacement.

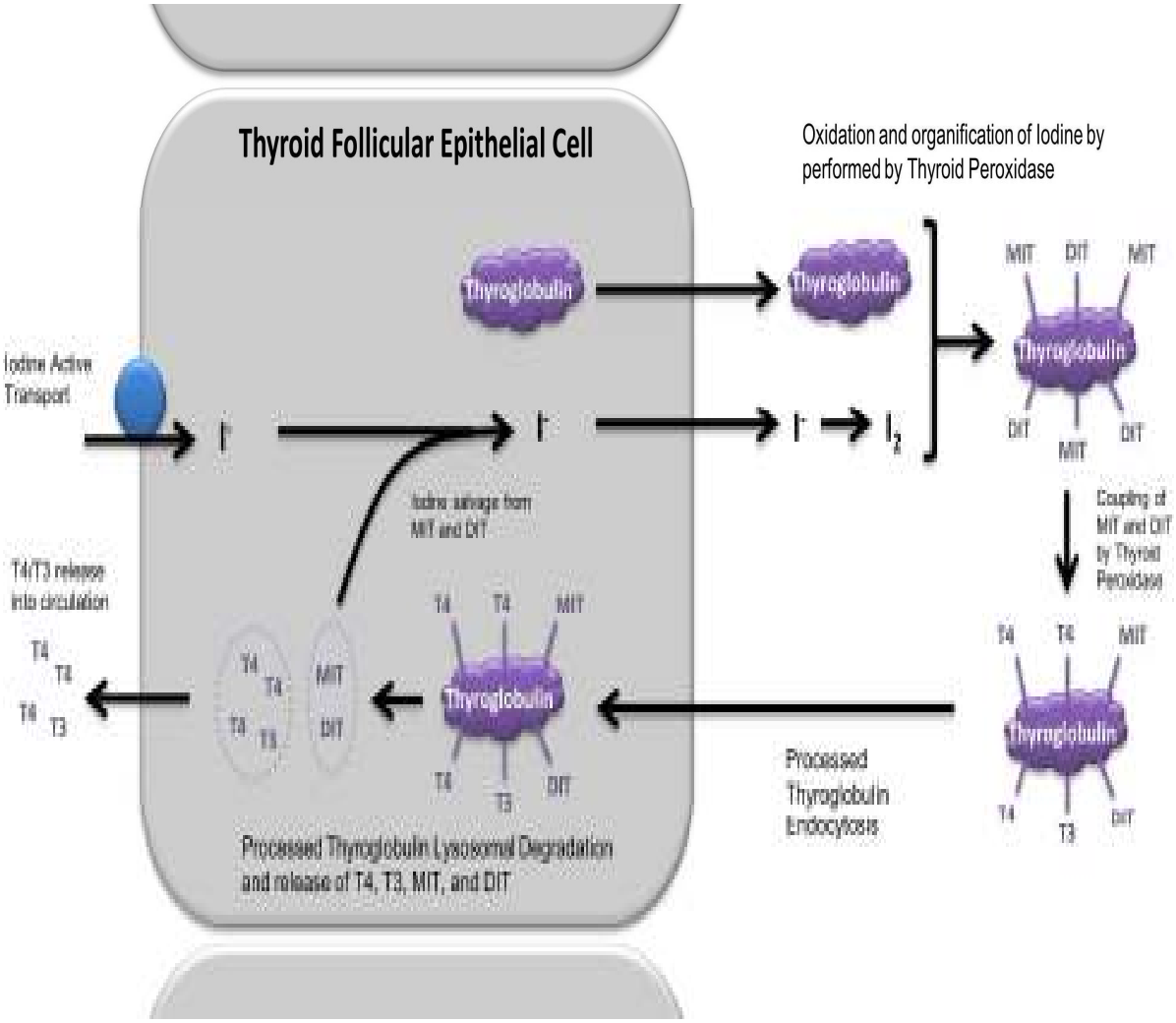

Figure 8 : Thyroid hormone synthesis

MECHANISM OF ACTION:

Thyroid hormone enters the cell and the T3 gets bound to thyroid receptors located inside the nuclei. TR is of two types TR alpha and TR beta. TR alpha is abundant in brain, kidneys, muscle, gonads and heart and the TR beta is present in pituitary and liver. T4 can also get bound but the binding is not as avid. The hormone receptor complex is then bound to the DNA via the Zinc fingers thus regulate expression of different genes that code for enzymes and thus regulates cell function. T3 binds with receptor 10–15 times greater affinity than T4, which explains its increased hormonal potency. T4 is produced in excess of T3 but receptors are occupied mainly by T3.

Regulation of the Thyroid Axis

TSH, secreted by anterior pituitary controls the thyroid axis and hence is a useful marker of thyroid hormone action. The thyroid axis is a feedback loop. Hypothalamic TRH stimulates the pituitary for the production of thyroid stimulating hormone, which, then stimulates the synthesis and secretion of the thyroid hormone. The thyroid hormones act mainly via TR beta and is fed back to cause inhibition of TRH and TSH secretion. The SET POINT in the axis is thus established by the thyroid stimulating hormone and TRH being the most important positive regulator of TSH synthesis and secretion.

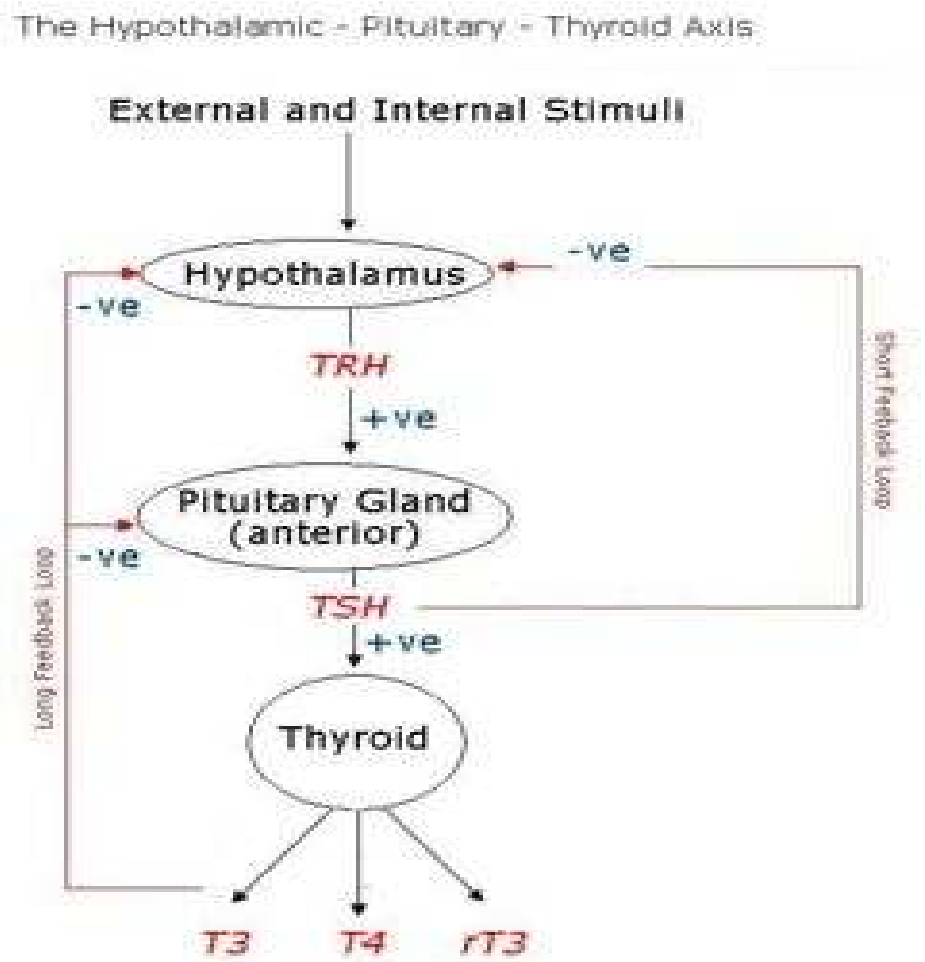

Figure 9 : Hypothalamic – Pituitary – Thyroid Axis

Like other pituitary hormones, TSH is released in a pulsatile maner and exhibits a diurnal rhythm and the highest level of TSH secretion occurs at night. TSH has a relatively long plasma t ½ that is around 50 minutes. TSH is measured using immunoradiometric asays that are highly sensitve and specific. TSH is used in the diagnosis of hyperthyroidism where there is low TSH and also hypothyroidism where there is high TSH.

The TSH is extremely sensitive to the levels of thyroid hormones in circulation and can be used as a useful tool in detection of thyroid abnormalities rather than using T4 or T3 levels. The thyroid dysfunction is classified as hypothyroidism, hyperthyroidism, subclinical hyperthyroidism depending upon the TSH and thyroid hormone levels.

Table 2: Thyroid dysfunction classification

Thyroid status	TSH	Thyroid hormone
Normal	Normal	Normal
Hypothyroidism	High	Low
Hyperthyroidism	Low	High
Subclinical hypothyroidism	High	Normal
Subclinical hyperthyroidism	Low	Normal

HYPOTHYROIDISM

Hypothyroidism is due to decreased effect of thyroid hormones on tissues. [42] The incidence is approximately 1% to 2%.[43] The serum TSH level greater than 10mU/L is associated with decreased thyroid hormone status.

Hypothyroidism is of two types primary and secondary

Table 3 : PRIMARY HYPOTHYROIDISM

Autoimmune	Hashimoto's and atrophic thyroiditis
Iodine deficiency	Environmental or nutritional
Iatrogenic	I 131 use, thyroidectomy radiation therapy to neck
Medications	Amiodarone, Lithium, antithyroid drugs
Congenital	Absent or ectopic thyroid Dyshormonogenesis TSH receptor mutation
Infiltrative disorder	Amyloidosis, Sarcoidosis scleroderma Hemochromatosis
Transient	Silent thyroiditis

Table 4: SECONDARY HYPERTHYROIDISM

Hypopituitarism	Tumors, Pituitary surgery Irradiation, Sheehans syndrome
Hypothalamic disease	Tumors, Trauma, Infiltrative disorder

Table 5 :Clinical features of hypothyroidism

Symptoms	Signs
Weakness, Tiredness	Carpal tunnel syndrome
Dry skin, hair loss	Dry coarse skin, Diffuse alopecia
Cold intolerance	Cold peripheries
Poor concentration and memory, Paraesthesia	Delayed DTR, Pseudomyotonic reflex
Weight gain and poor appetite	Puffy hands and feet
Constipation	
Dyspnoea	Pericardial and pleural effusion
Hoarseness	
Menorrhagea	

HYPERTHYROIDISM

Hyperthyroidism[45] is due to excessive action of thyroid hormones in the body tissues. Thyrotoxicosis is a synonym. Grave's disease is the commonest cause of hyperthyroidism. Approximately 0.5% to 1% of the population suffers from hyperthyroidism. The TSH levels are suppressed, <0.1mU/L and associated with high levels of thyroid hormones. It is of 2 types that is primary and secondary, the different causes of each is included in the table below.

Table 6: HYPERTHYROIDISM

Primary hyperthyroidism	**Secondary hyperthyroidism**
Graves disease	TSH secreting pituitary adenoma
Toxic MNG	Thyroid hormone resistance
Toxic adenoma	Gestational thyrotoxicosis
Thyroid malignancy	
Thyrotoxicosis + hyperthyroidism	
Subacute granulomatous thyroiditis	
Silent thyroiditis	

Table 7 : CLINICAL FEATURES OF HYPERTHYROIDISM

SYMPTOMS	SIGNS
Hyperactive	Tremors
Irritable	Goitre
Dysphoria	Warm moist skin
Palpitation	Tachycardia and atrial fibrillation
Fatigue	Lid retraction lid lag
Weight loss and increased appetite	Tachycardia
Diarrhoea	Proximal muscle weakness
Polyuria	
Oligomenorrhoea ,loss of libido	Gynaecomastia

SUBCLINICAL HYPOTHYROIDISM

According to the latest consensus statement by the American asociation of clinical endocrinologists , the American thyroid association and the endocrine society , subclinical hypothyroidism[46] is defined as an elevated serum TSH level(4.5mU/L to 10mU/L) asociated with normal total or free T4 and T3 levels. Overall the prevalence is 2% to 8% → general population[41]

SUBCLINICAL HYPERTHYROIDISM

Subclinical hyperthyroidism is defined as low serum TSH levels (0.1mU/L to 0.4mU/L) asociated with normal T4 and T3 levels.[40] Subclinical hyperthyroidism prevalence is about 2%. Most often subclinical disease is asymptomatic but some patients show symptoms of deficiency of thyroid hormone in subclinical hypothyroidism.

SICK EUTHYROID SYNDROME

Thyroid hormone alteration occurs in many diseases which affect mainly the T3 level in the absence of any intrinsic thyroid glandular disease. It is also called Low T3 syndrome, Non thyroidal illness syndrome or Thyroid hormone adaptation syndrome. Sick euthyroidism syndrome occurs in the following conditions

- Acute critical illness – life threatening infections or Myocardial infarction
- Burns or polytrauma
- Post operative period
- Diabetes mellitus
- Renal diseases
- Liver disease
- Malignancy
- Patients on chronic steroid therapy , phenytoin use

Sick euthyroid syndrome is most often associated with fall in total and free T3 with normal T4 and TSH. The magnitude of fall in the T3 correlates with the severity of the disease. In this condition the peripheral conversion of T4 to T3 by deiodinase is abnormally low and instead is converted to Reverse T3. This is one mechanism although the main mechanism is decreased clearance than production for increased rT3. T4 by alternate metabolism is converted to inactive T3 sulfate. With increase in disease severity there is decrease in serum T4 also called the low T3 T4 syndrome. Though T level falls the free T4 remains within normal limits or slightly on the lower side. T3 T4 even if is lower, serum TSH levels are normal or reduced , this is the main difference from primary hypothyroidism where TSH level rises with fall in T3 T4 levels.

LABORATORY EVALUATION

- Estimation of Thyroid Hormones

TSH levels change in response to changes in T3 and T4 , so initial determination of TSH is to be first done. If TSH is abnormal then measurement of T3 T4 to confirm diagnosis of hyperthyroidism or hypothyroidism. In hyperthyroidism TSH level is low due to feedback inhibition by elevated T3 T4. In hypothyroidism TSH level is high. Radioimmunoasay is used for serum total T4 and total T3 estimation.

T4 and the T3 are greatly bound to proteins and this protein binding is affected by many factors like medications pregnancy or genetic make up. So it is useful to measure free T3. Moreover in pregnancy there is increase in thyroid binding globulin which leads to increase in total thyroid hormone levels similarly when there is decrease in thyroid binding globulin as in nephrotic syndrome, total thyroid hormone level is decreased.

- Tests to determine Thyroid Dysfunction etiology

TPO antibodies: autoimmune thyroid disease is detected by measuring antibodies versus Thyroid peroxidase and thyroglobulin. It is found that around 10 % of euthyroid women and 2 % of euthyroid men have thyroid antibodies. In autoimmune hypothyroidism TPO antibodies is universally found whereas in graves disease upto 80 % have this.

THYROID STIMULATING ANTIBODIES : These stimulate the TSH-R in Graves disease.

THYROGLOBULIN LEVELS : It is elevated in thyrotoxicosis of all kinds except thyrotoxicosis factitia. Thyroglobulin levels are increased in thyroiditis. n of thyroid hormone.

RADIOIODINE UPTAKE AND THYROID SCANNING: The thyroid gland selectively transports radioisotopes of iodine - (123I, 125I, 131I)

Nuclear imaging of Graves disease is found to have increase in size of the gland and more tracer uptake .Thyroid scan has also role in monitoring patients with thyroid cancer.

d) Thyroid Ultrasound

USG is used in the diagnosis of nodular thyroid disease.

MANAGEMENT

Hypothyroidism:

- Levothyroxine [47] is the treatment of choice. Levothyroxin is converted to thyroxin in the body. It is partially, the more active thyroid hormone. If there is no residual thyroid function, the daily replacement dose of levothyroxine is usualy 1. 6 microgram/kg body weight (typicaly 10–150 microgram).

- Adult patients who are less than sixty years without evidence of heart disease may be started on 50-100 microgram levothyroxine (T4) daily.

- The dose adjustment is based on TSH levels, with target of normal TSH. TSH response is slow and so should be repeated almost 2 months after starting levothyroxin or change of dose.

Hyperthyroidism :

The hyperthyroidism of Graves' disease is treated by decreasing the synthesis of the thyroid hormones using the drugs called antithyroid medications and by decreasing the thyroid tissue by radio- iodine ablation or by thyroidectomy. Antithyroid drugs are propylthiouracil, carbimazole and its active metabolite methimazole. All of these block TPO enzyme , thus reducing oxidation of and organification of the iodide molecule.

- Propylthiouracil[47] blocks deiodination of T4 to Triiodothyronine
- The starting dose of carbimazole or methimazole is usually 10–20 mg every 8 or 12 h, and changed to daily once dosage after euthyroidism is attained.
- Propylthiouracil is given at a dose of 10–20 mg once in 6–8 hours
- TFT and clinically patient is reviewed 3–4 weeks after initiating therapy and then the dose is altered based on the free T4 levels.
- It takes about six to eight weeks after therapy initiation to achieve euthyroidism
- TSH levels often remain suppressed for several months and therefore do not provide a sensitive index of treatment response.

- The usual daily maintenance doses of antithyroid drugs in the titration regimen are 2.5–10 mg of carbimazole or methimazole and 50–100 mg of propylthiouracil.

- In the block-replace regimen, the initial dose of antithyroid drug is held constant, and the dose of levothyroxine is adjusted to maintain normal unbound T4 levels. When TSH suppression is alleviated, TSH levels can also be used to monitor the effectiveness of treatment

- Maximum remission rates of up to 30– 50% are achieved by around 2 years for the titration regimen and by 6 months for the block-replace regimen.

- Propranolol (20–40 mg Q6H) or atenolol, are used for controlling the adrenergic symptoms mostly in the early stages of diseases before the antithyroid drugs action becomes effective.

- Radioiodine acts by destroying thyroid cells and may be used as a initial therapy or for relapse after a trial with the antithyroid drugs.

- Subtotal or near-total thyroidectomy is an option for patients who relapse after antithyroid drugs

THYROID DYSFUNCTION IN HIV DISEASE

HIV disease is associated with many endocrine abnormalities. Many of these occur in early and many in late stage of the disease. Among those with HIV disease around 2 % develop frank thyroid illness. But what is more prevalent is subtle dysfunction in thyroid[48]. Thyroid profile derangements are common in HIV patients. Thyroid binding globulin level is raised in them and there is inverse correlation with CD 4 count.[49] Abnormal TFT may be due to the stress of the disease in patients with advanced disease. Subclinical hypothyroidism is common among the adult HIV infected patients. Abnormal TFT results may be caused by the stress of illness in patients especially those with low CD 4 counts. Thyroid dysfunction has been reported with the use of HAART.

PATTERNS OF THYROID DYSFUNCTION

Hypothyroidism

Frank hypothyroidism affects approximately 0.3 % of general population. Among HIV infected individuals the prevalence is about 0.1 to 2.6%. The commonest etiology of hypothyroidism is autoimmune .In patients with HAART induced IRIS hashimotos is rare. Levothyroxine replacement is done to treat patients with symptomatic hypothyroidism with the aim of maintaining the TSH level at around 0.5–2.5 mU/L.

SUBCLINICAL HYPOTHYROIDISM

The prevalence of subclinical hypothyroidism is 4.3% in the general population. Anti TPO antibodies are positive in 50 to 80 % of them Subclinical hypothyroidism[51] is prevalent in HIV patients particularly the patients on antiretroviral drugs approximately 3.5 to 12.2% . In these patients anti TPO antibodies are not commonly seen. This may point to the fact that it may not be due to autoimmunity. In treating subclinical hypothyroidism, patients without HIV infection, serial TSH estimation once in 1 to 3 months is needed as the levels may become normal in a year in almost one third of the patients. But in those with HIV infection such normalization is not seen. If there is persistently increased thyroid stimulating hormone level patients need to be treated with levothyroxine . Now the guidelines say that in general population treatment is to be offered in those with TSH level more than10 mU/L and individual patient wise decision regarding treatment in those who have TSH values 4.5–10 mU/L in the sense that those with symptoms of thyroid abnormality or who have anti TPO antibody be treated. Patients who are not on levothyroxine, its recommended to do TSH estimation every half yearly to yearly to determine progression.

Isolated decreased FT4 levels

Decreased Free T_4 levels along with normal TSH levels are found in HIV patients, with prevalence which is of 1.3%–6.8%. In adults didanosine stavudine and also the drug ritonavir are associated with this pattern of thyroid profile. Decreased free T4 may be due to the hypothalamus or the anterior pituitary dysfunction. In one study TSH releasing hormone when administered to those with decreased free T4 had no delayed and no absent TSH release, thus ruling out pituitary or hypothalamic dysfunction as a cause of decreased free T4. Those taking antiepileptic drugs had low free T4 possibly due to artifact due to the intereference of the drug in the estimation of the free T4. The patients with low free T4 do not have signs and symptoms of hypothyroidism hence the significance of free T4 clinically is not very clear.

TFT abnormalities due to nonthyroidal illness.

Low thyroid hormone levels in HIV patients, the possibility of Sick Euthyroid Syndrome needs to be considered. It is also called as non thyroidal illness. When anyone is suffering from any severe illness of which AIDS is one of the kind the deiodinaation of thyroid hormone T4 is impaired. So there is no enough production of triiodothyronine and no reverse T3 metabolism instead 5' deiodination of T4 to the inactive hormone called reverse T3 occurs which virtually creates a TFT

abnormality pattern. But this TFT abnormality is due to body's response to severe illness rather than due to thyroid glandular function abnormality. Since AIDS due to the above described process can produce abnormal TFT this should be kept in the mind when interpreting TFT in patients with advanced HIV infection. Decreased triiodothyronine and elevated RT3 and variable free T4 and a low or normal thyroid stimulating hormone level , different patterns based on the grades of severe illness.

When the patient improves the thyroid stimulating hormone level rises and in some it rises above the normal level as both free T4 and triiodothyronine come back to baseline and this is similar to subclinical hypothyroidism pattern.

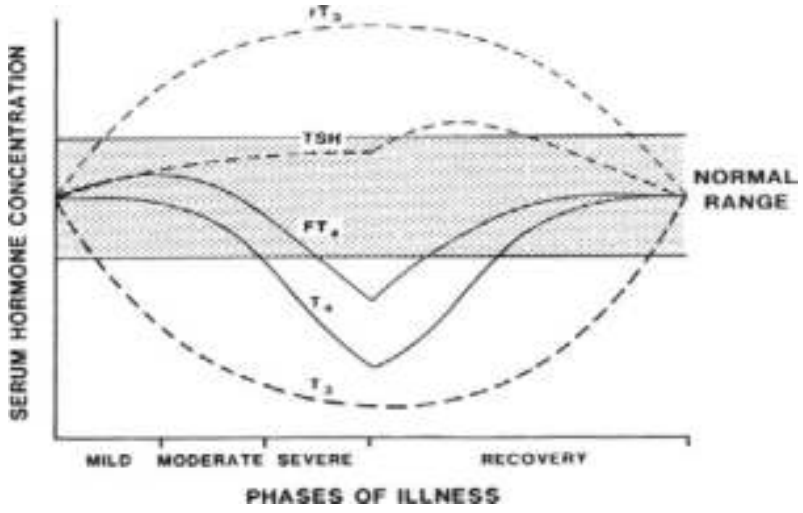

Figure 10 : TFT Results in sick euthyroid syndrome

Sick euthyroidism was most prevalent approximating 16 % in those with advanced AIDS before highly active antiretroviral therapy became extensively used.

Treatment of sick euthyroidism requires treatment of the underlying severe disease and not hormone replacement. Repeat TFT after 1 to one and half months after the severe illness is controlled with HAART confirms the diagnosis.

CONDITIONS CAUSING THYROID FUNCTION ABNORMALITIES IN AIDS

- Opportunistic infection and malignancies cause thyroid dysfunction in AIDS
- Thyroditis due to Pneumocystis jiroveci and Cryptococcus neoformans
- Bacterial infection leading to suppuration of thyroid gland
- Infiltration of the gland with lymphoma or kaposi sarcoma .

Hyperthyroidism

Symptoms of hyperthyroidism along with increased T3 T4 and decreased TSH is classical of hyperthyroidism. The autoimmune disorder called as the Graves disease is characterized by the formation of

antibodies to TSH receptor is the most common etiology of hyperthyroidism in general as well as HIV infected individuals. The IRIS which occurs after highly active retroviral therapy initiation is the state at which graves usually occurs in HIV infected patients. The IRIS causing exacerbation of Mycobacteria tuberculosis and and other infection usually occur in almost three months of antiretroviral therapy initiation. Where as the graves disease occurs approximately one to three years after starting highly active antiretroviral therapy. It is found that CD4 count increases in two phases after highly active antiretroviral therapy is started. One is by CD4 memory cells getting redistributed from the lymphoid organs and second phase occurs many months afterwards when there is increase in naïve CD 4 lymphocytes.

BIPHASIC INCREASE IN CD 4 CELLS DURING IRIS

Phase 1

- CD 4 cells redistributed from lymphoid organs

Phase 2

- Increase in Naive CD 4 cells

In patients with TFT patterns of overt hyperthyroidism radioiodine uptake study and the scanning of the thyroid gland can discriminate between the different etiologies of hyperthyroidism. In Graves there is increased uptake of radioiodine and shows homogenous pattern by scan whereas in MNG thyroid or thyroid adenoma shows increased radioiodine uptake but heterogenous .

Decreased radiiodine uptake is found in thyroiditis both subacute granulomatous and painless thyroiditis. Subacute granulomatous thyroiditis occurs after respiratory tract infection by some viruses causes increased thyroid hormone state initially, then around a month or a month and a half later causes decreased thyroid hormone status. Painless thyroiditis is an autoimmune thyroid inflammation which is quite often transient and has anti TPO antibodies.

Treatment of hyperthyroidism

Graves' disease can be treated with antithyroid drugs to decrease production of thyroid hormone. Radioiodine ablation of the thyroid gland or surgical treatment is the definitive treatment for graves disease and also for MNG and toxic adenoma.

Subacute thyroiditis is treated with NSAID s and if not cured with steroids for pain. Beta blockers relieve the adrenergic symptoms. Painless thyroiditis only treatment is beta blockers.

Subclinical hyperthyroidism

Subclinical hyperthyroidism predate hyperthyroidism and is characterized by decreased TSH, normal free T_4 and T_3 levels, and no symptoms of thyrotoxicosis. If symptoms are there then antithyroid medication or ablation of gland with radioiodine may be required. subclinical hyperthyroidism can lead to the following complications – atrial fibrillation and decreased mineral density of the bone . So it is told to treat those patients with the TSH level less than 0.1 mU/L or are elderly that is more than 60 years or those with osteopenia. Treatment is not needed as per guidelines in those with milder disease that is thyroid stimulating hormone level of 0.1 to 0.45 mU/L and guidelines ask for repeated TFT half yearly or yearly.

HAART and thyroid dysfunction [76]

HAART, particularly stavudine, is associated with a high prevalence of subclinical hypothyroidism. Hypotheses are made regarding responsible mechanisms and risk factors. Thyroid function should be tested and sequentially rechecked in HAART patients.

ROLE OF SCREENING THYROID FUNCTION TEST IN THYROID DISEASE

- Older patients may be screened for thyroid dysfunction as there is increased incidence of subclinical hypothyroidism
- TSH level measurement in those with symptoms of thyroid function abnormalities or decreased bone mineral density or altered lipid profile or depression or atrial fibrillation.
- If TSH is found to be elevated FT4 is to be estimated
- If TSH is low , Both free T4 and T3 need to estimated to rule out T3 toxicosis
- Sick euthyroidism is to be considered in the interpretation of altered thyroid function test especially in advanced HIV disease

Correlation with the type of thyroid dysfunction observed:

Belttrans et al[52] studied 350 HIV+ patients showing that

- 16% suffered from hypothyroidism
- Subclinical hypothyroidism → 6.6 %

hypothyroidism was predominating among the advanced HIV disease and the subclinical hypothyroidism was dominant in other stages of the HIV.

Jain G et al → a prevalence study which included fifty HIV patients at different stages of illness. Patients were divided into two groups[53]

- Group-1 had 25 patients those who had AIDS
- Group-2 had 25 patients who were HIV+ but who were not having AIDS
- 18% had free T 3 levels below the normal range
- 20% patients had decreased FT-4 levels
- 24% patients had TSH levels above the normal range.
- 20% of those who had hypothyroidism were found to be among the AIDS patients
- subclinical hypothyroidism predominated among the HIV infected who did not have AIDS

Sunder S et al studied 150 HIV patients. [59]

They divided the study group into 3

- These patients were divided in three
- Group A → CD4 < 200 /microlitre
- Group B → CD 4 200 – 350 / microlitre
- Group C → CD 4 >350 / microlitre

- In group A, fifteen of them had subclinical hypothyroidism and eleven had overt hypothyroidism.
- In group B, 18 had subclinical hypothyroidism and 4 had overt hypothyroidism.
- In group C, 12 patients had subclinical and 1 had clinical hypothyroidism

hypothyroid as well as subclinical hypothyroid states were seen in advanced HIV, and in non-AIDS groups, subclinical hypothyroid state was dominant [55,56]

Palanisamy et al[57]

Studied alteration in thyroid function in AIDS patients in relation to infection with HIV and healthy subjects.

- No statistically significant difference in the thyroxin concentrations in those with AIDS was found in comparison to those with HIV infection and those who are healthy subjects.
- FT4 concentration was statistically significantly decreased in HIV and those with AIDS
- Total triiodothyronine concentrations were normal in those infected with HIV and slightly decreased in those with AIDS

- T3 level was decreased in AIDS patients.
- The level of FT3 was slightly but significantly raised in HIV infected and significantly decreased in those with AIDS
- The study concluded that thyroid dysfunction is frequent in HIV infection and with progression of disease there is a primary hypothyroid like stage that occurs in patients with HIV infection.

Relationship with ART[59,60,61]

Beltran et al study 350 HIV patients for thyroid dysfunction. 32% had thyroid dysfunction. In a substudy ,age and sex matched groups of patients naïve of ART and those on ART were studied for changes. They found no difference between the 2 groups which were statistically significant.

Bongiovanni et al [58]observed statistically significant changes, in the form of increased cases of subclinical hypothyroidism(15%) in the patients receiving HAART.

Calaza L et al [62] Eighty-four patients were evaluated for the study, including 49 subjects treated with HAART and 35 naive to antiretroviral agents. Subclinical hypothyroidism (defined as an increase of TSH levels associated with normal T3 and T4 levels), was detected in 6 patients out

of 49 subjects on HAART (12.2%), while no case of dysthyroidism was observed in the group of antiretroviral-naive patients ($p<0.05$). A long prior exposure to HAART was reported in all patients (ranging from 27 to 58 months), and ongoing antiretroviral therapy included stavudine in all the 6 cases, lamivudine in four, didanosine in two, saquinavir in three, indinavir, nelfinavir and lopinavir/ritonavir in one case each; duration of HAART ranged from 21 to 41 months.

Relationship with CD4 counts[63,64]

Most study series have found an inverse correlation of the CD4 counts with TSH values. There were no conclusions drawn in relation to their clinical manifestations in the different stages according to CD4 count.

Sunder et al, studied patients in 3 groups(CD4<200cells/mm3,200-350cells/mm3 and >350cells/mm3). Each group had 50 subjects. Percentage of low TSH was maximum amongst subjects with CD4 <200cells/mm3(52%) and least amongst those with CD4 > 350 cells/mm3 (26%). All the studies owe this inverse correlation to the immune reconstitution occurring with advanced disease or the institution of ART.

Beltran et al, had 2 groups, A:CD4 >200 cells/mm3 and B:CD4<200cells/mm3,it found 67.8% hypothyroid in group A and 32.2%

in group B. Low CD4 cell count was a risk factor for hypothyroidism in the present study. [38]

Madge S et al [65,66]

It was a retrospective analysis of thyroid function test in HIV patients. The prevalence of and factors which are associated with both the clinical and the subclinical thyroid dysfunction were studied. Those patients who had normal thyroid function tests but had thyroid disease in the past were found from the medical records department and was made part of the overt category.

- 73% of the clinic population had at least one thyroid function test done since 2001.
- 1233 (79%) were male
- 1043 (66%) were white
- 365 (23%) were black African
- 969 (62%) - the main risk factor for HIV was homosexual mode of transmission
- Median age of the study was 37 years.
- Nine hundred patients (58%) - on highly active antiretroviral therapy when the study began.

Table 8 : Madge S et al results

➢ Thyroid dysfunction	➢ Percentage affected
➢ Overt hypothyroidism	➢ 2.5 %
➢ Overt hyperthyroidism	➢ Less than 1 %
➢ Subclinical hypothyroidism	➢ 4 %
➢ Subclinical hyperthyroidism	➢ <1%
➢ Sick euthyroidism	➢ 17%
➢ Euthyroidism	➢ 75.5 %

- By Multivariate analysis : no independent variable had statistical association with overt hypothyroidism . [68,69]

MATERIALS AND METHODS

Research Design:

The present study is an observational and prospective study.

Source of data:

Patients admitted to and those attending Coimbatore medical college hospital as out patients who are newly diagnosed as HIV positive as per NACO March 2007 criteria.

Methodology

Sample size – fifty

Sampling method – simple random sampling

Fifty patients who were diagnosed to have HIV infection according to National AIDS Control Organisation (NACO) March 2007, who fulfilled the inclusion and exclusion criteria who got admitted to coimbatore medical college hospital or attended Out patient department from september 2013 to february 2014 and who gave consent to be part of the study were included in the study. Data was collected by using pre-tested proforma meeting the objectives of the study. All enrolled patients were investigated for thyroid dysfunction by measuring total T3, total T4, TSH adetailed history and clinical examination. Thyroid function

abnormalities were compared with HIV status, CD4 count and WHO clinical stage of HIV disease. Patient confidentiality was maintained.

INCLUSION CRITERIA:

Newly diagnosed HIV seropositive patients by ELISA testing by NACO March 2007 guidelines in the age group 20 to 60 years

EXCLUSION CRITERIA

1. Patients already known thyroid disease
2. Patients already on Thyroxin treatment.
3. Patient who had undergone thyroid surgery in the past
4. patients on drugs altering thyroid function – like

Amiodarone , Lithium, Phenobarbitone, Carbamazepine, Phenytoin , Para amino salicylic acid, Antiretroviral drugs especially stavudine.

5. Pregnant patients.

6. patients on oral contraceptive pills

Investigations done:

- HIV serology by ELISA
- CD4 count by Flow cytometry
- Thyroid function test T3 T4 TSH by electrochemiluminescence method
- Complete haemogram with ESR

- Renal function test
- Liver function test
- Chest X ray

Statistical analysis:

Statistical methods applied[67,68,69,70]

The data that was collected was subjected to descriptive statistical analysis. Results on continuous measurement were expressed as Mean and standard deviation and results on categorical measurements are presented in numbers and percentage. Chi square test was used to assess the significance of the results. Odds ratio was used when applicable. The results were considered significant if p value was below 0.05.

SOFTWARE used :

- Microsoft word 2007 and Microsoft excel is used to generate graphs and tables.
- The statistical software, SPSS 19.0 Med Calc 9.01 was used to analyse the data.

RESULTS

Table 9 : Age Distribution of the study group

Age in years	No: of patients	Percentage
20-30	8	16
31-40	24	48
41-50	11	22
51-60	7	14
Total	50	100

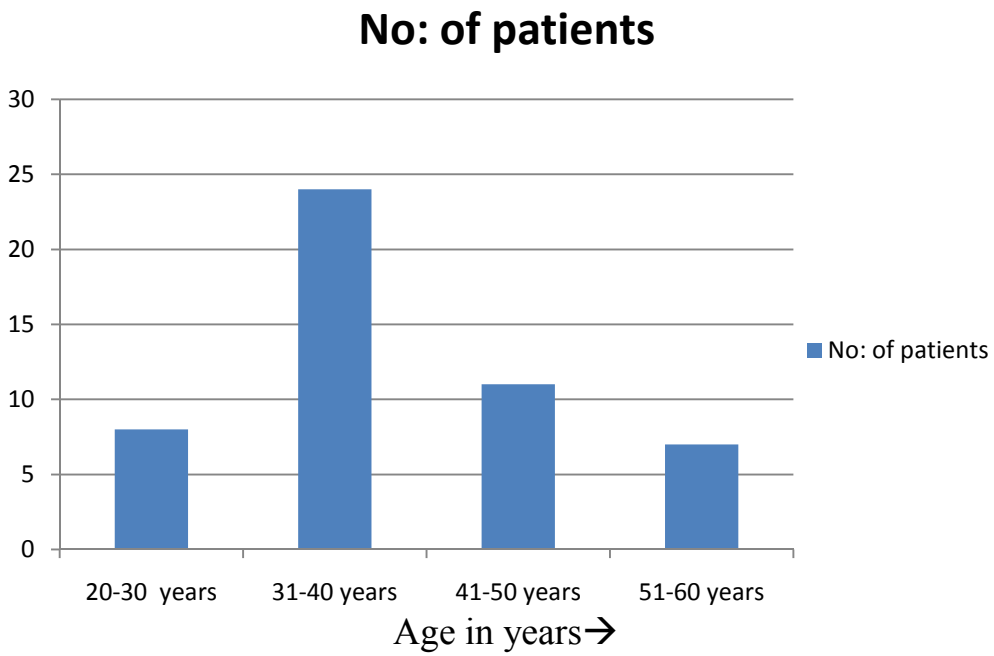

Figure 11 : Age distribution of patients in the study group

Table 10. : Sex wise distribution of Patients in study group

Sex	Frequency	Percentage
Male	20	40
Female	30	60
Total	50	100

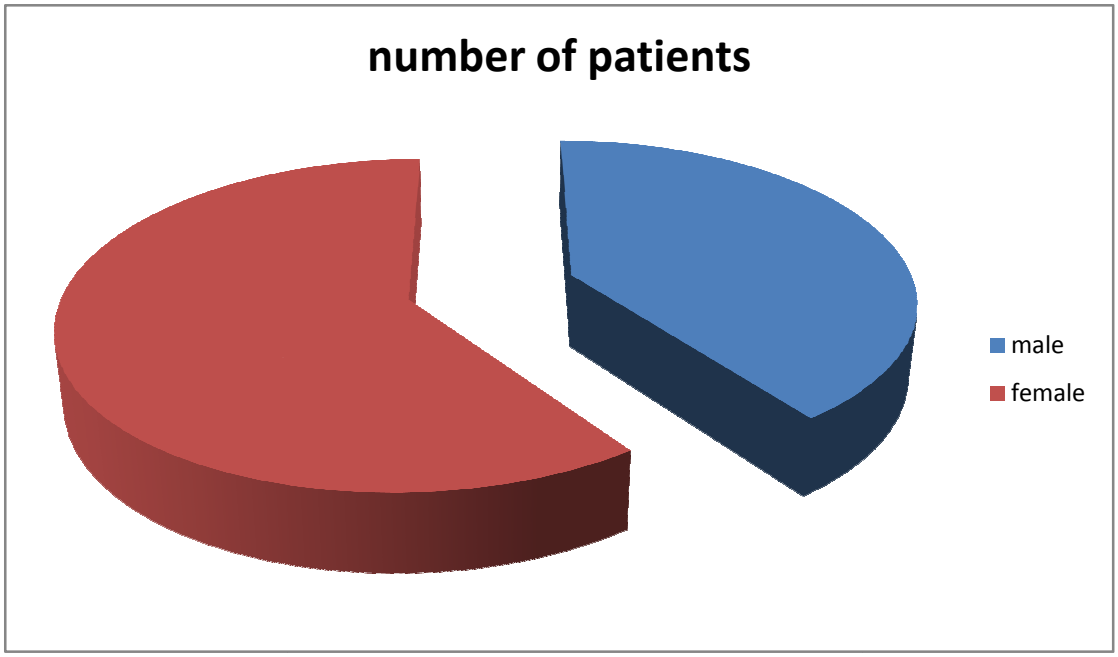

Figure 12. : Sex wise distribution of patients in study group

Table 11 : Mean of TFT and CD4 & Standard Deviation of the study group

	T3	T4	TSH	CD4
Mean	102.85	7.235	5.869	234.22
Standard Deviation	37.906	1.7343	6.2372	101.316

Table 12 : Thyroid status of the study group gross

	Frequency	Percentage
Euthyroid	31	62
Thyroid dysfunction	19	38
Total	50	100

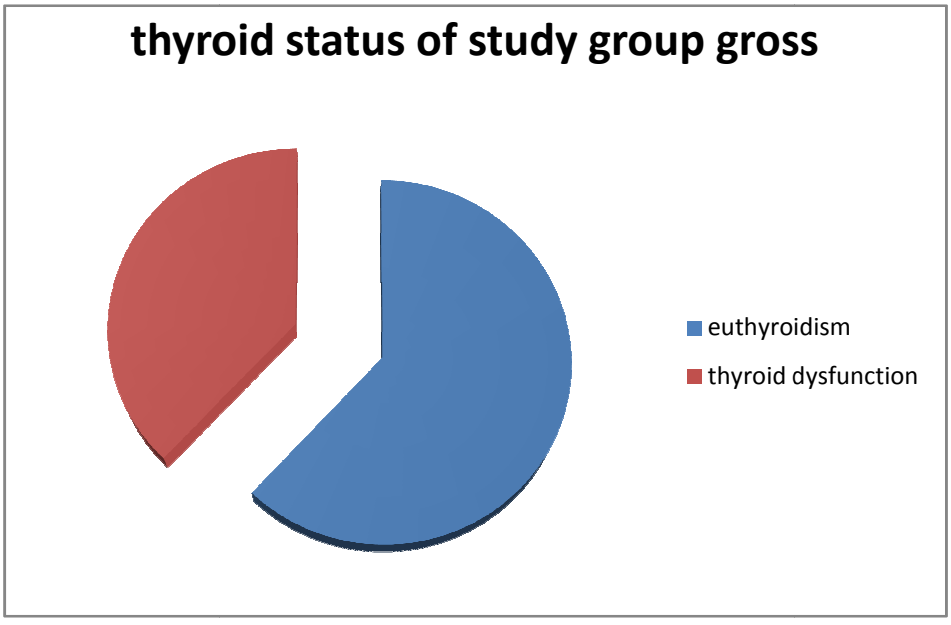

Figure 13. Thyroid status of the study group gross

Table 13 : Distribution of thyroid function in the study group

Thyroid status	Number of patients	Percentage
Euthyroidism	31	62
Subclinical hypothyroidism	10	20
Hypothyroidism	6	12
Hyperthyroidism	1	2
Low T3	2	4
Total	50	100

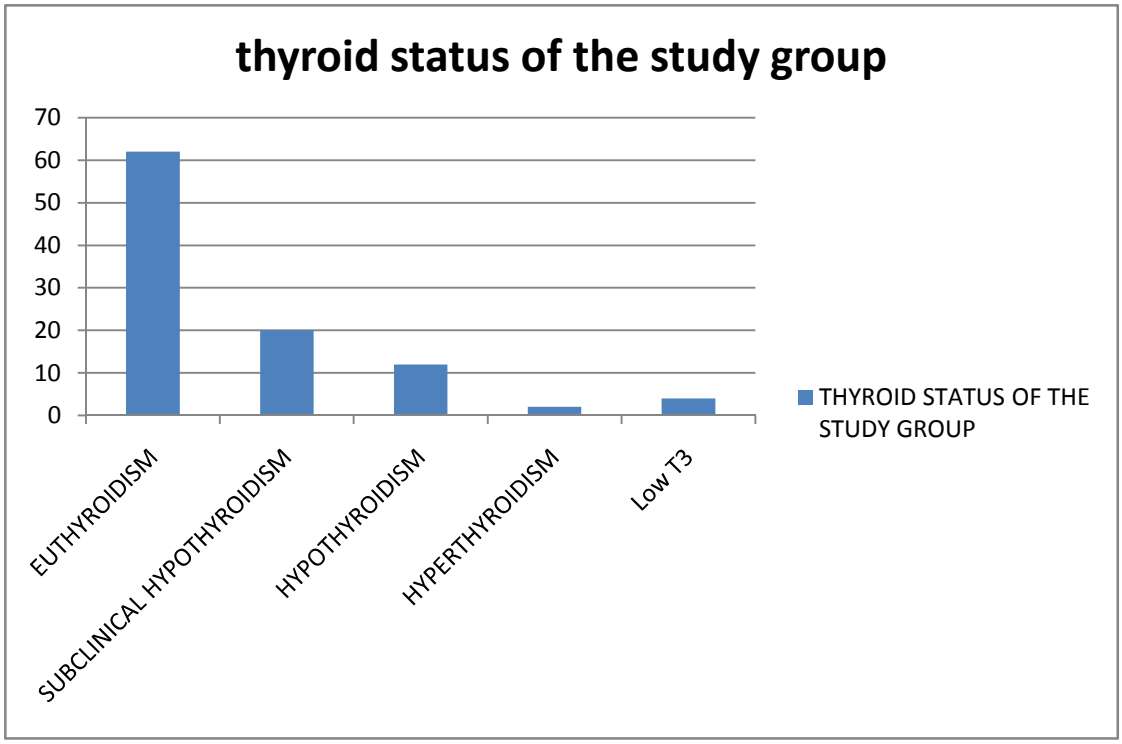

Figure 14 : Distribution of thyroid function in study group

Table 14 : Distribution of CD4 count of patients in study group

CD4 count	Number of patients	Percentage
<200	19	38
201-500	31	62
>500	0	0
Total	50	100

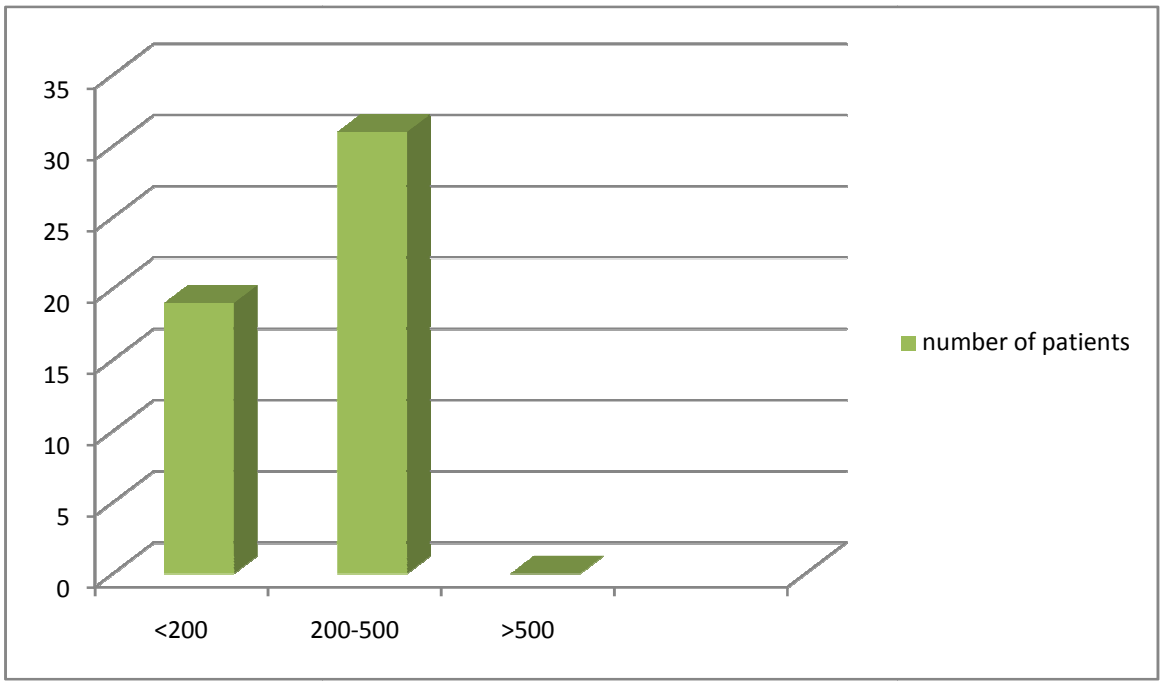

Figure 15: Distribution of CD4 count of patients in study group

Table 15 : Distribution of HIV patients based on WHO Clinical stage

WHO Clinical stage	Number of patients	Percentage
1	4	8
2	17	34
3	15	30
4	14	28
Total	50	100

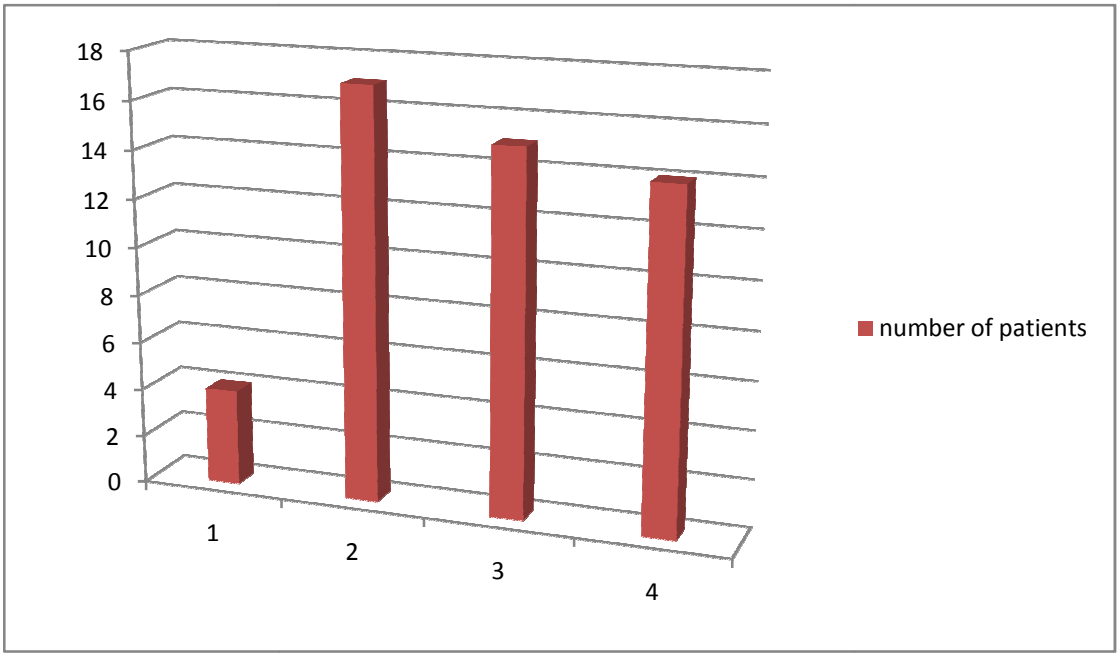

Figure 16 : Distribution of HIV patients based on WHO Clinical stage

Table 16 : Haemoglobin levels in HIV patients

Haemoglobin level	Number of patients	Percentage
<6	1	2
6.1 – 9	13	26
9.1 – 12	23	46
>12.1	13	26
Total	50	100

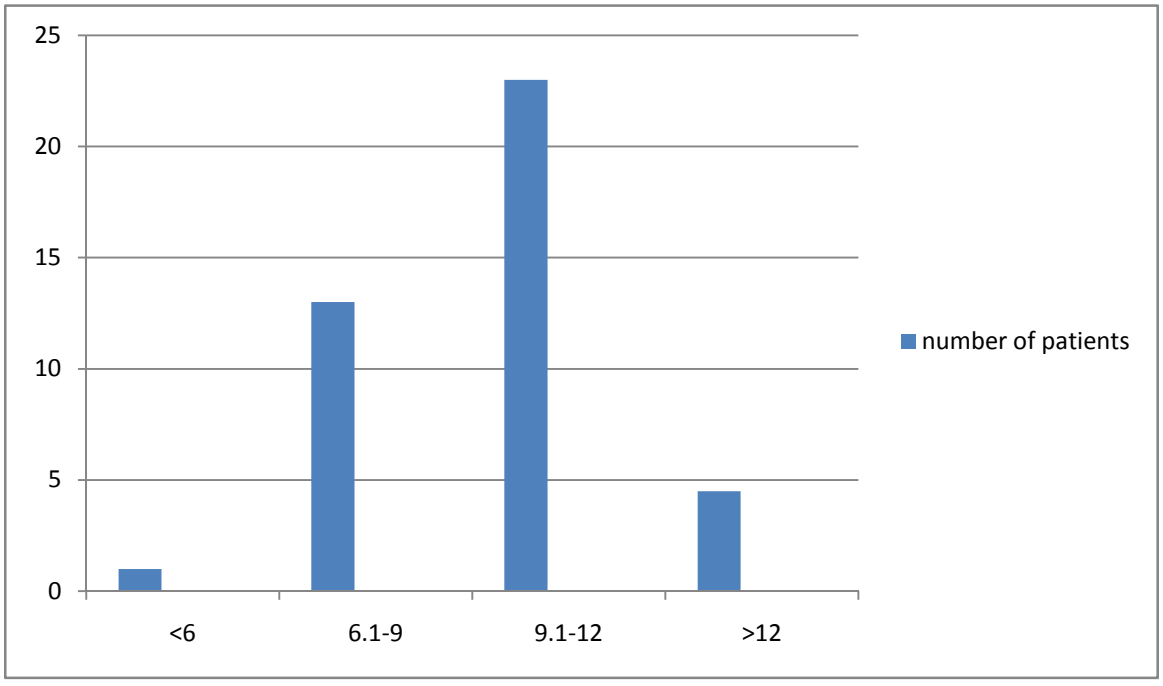

Figure 17 : Hemoglobin levels in HIV patients

Table 17 : Distribution of pallor in HIV patients

Pallor	Number of patients	Percentage
Present	24	48
Absent	26	52
Total	50	100

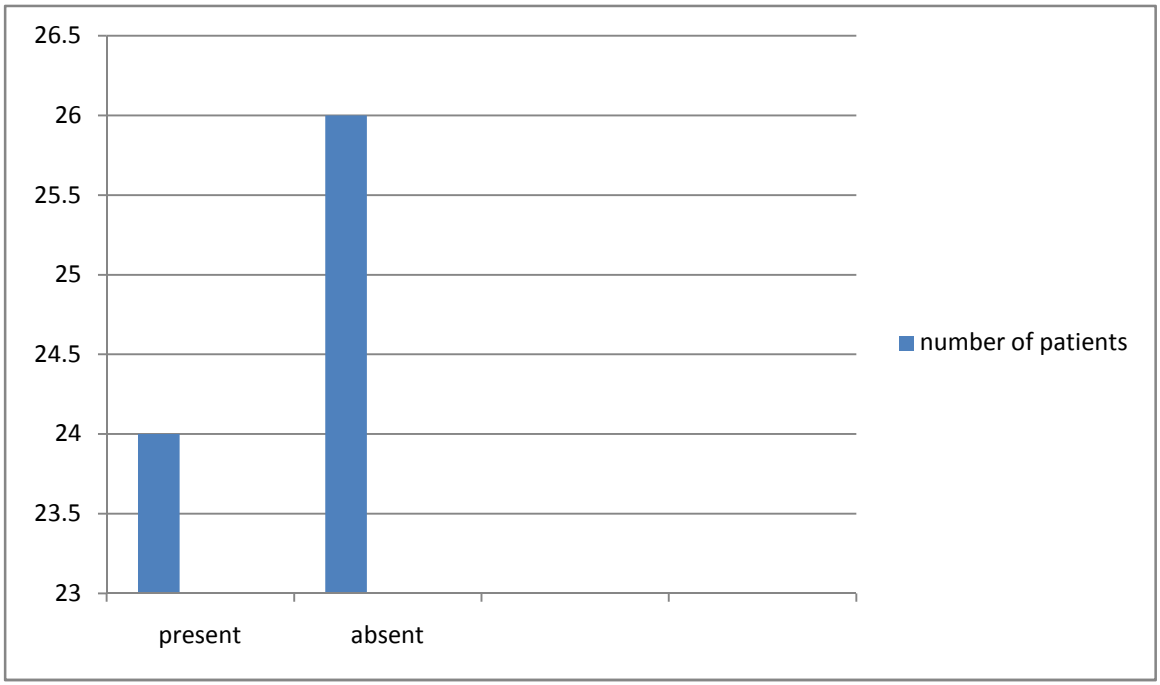

Figure 18: Distribution of pallor in HIV patients

Table 18: Distribution of oral candidiasis in HIV patients

Oral candidiasis	No : of patients	Percentage
Present	30	60
Absent	20	40
Total	50	100

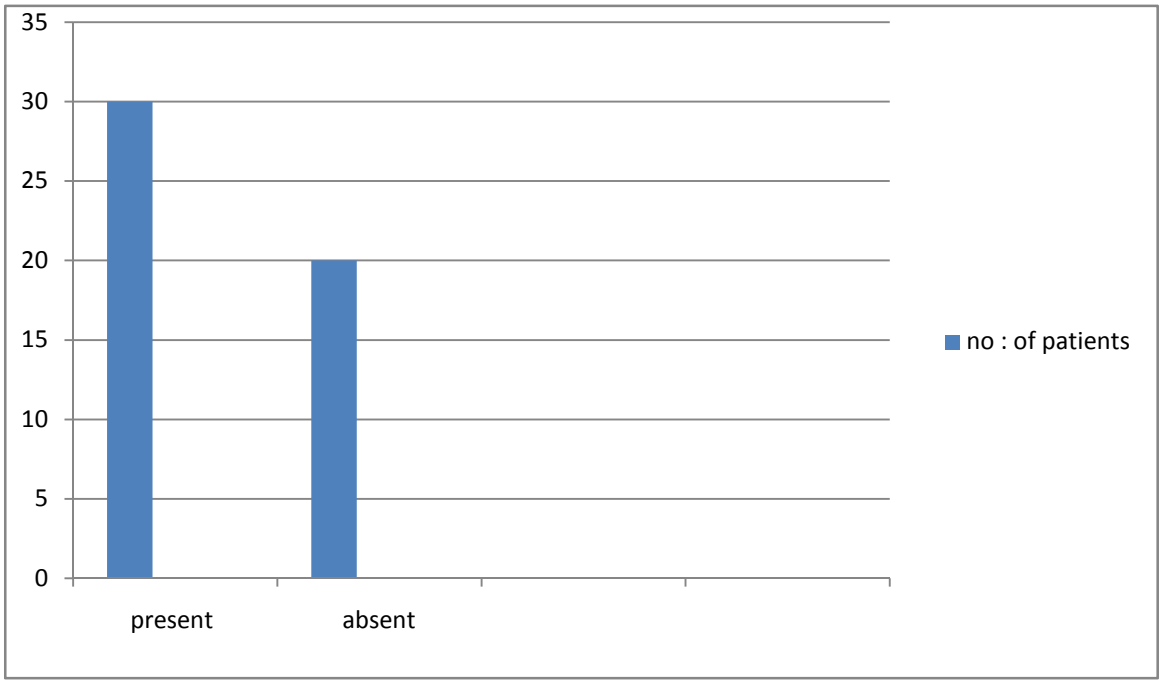

Figure 19: Distribution of oral candidiasis in HIV patients

Table 19: Association of Age With Thyroid Dysfunction

Age	Euthyroidism	Thyroid dysfunction
21-30	8	0
31-40	15	9
41-50	4	7
51-60	4	3
Total	31	19

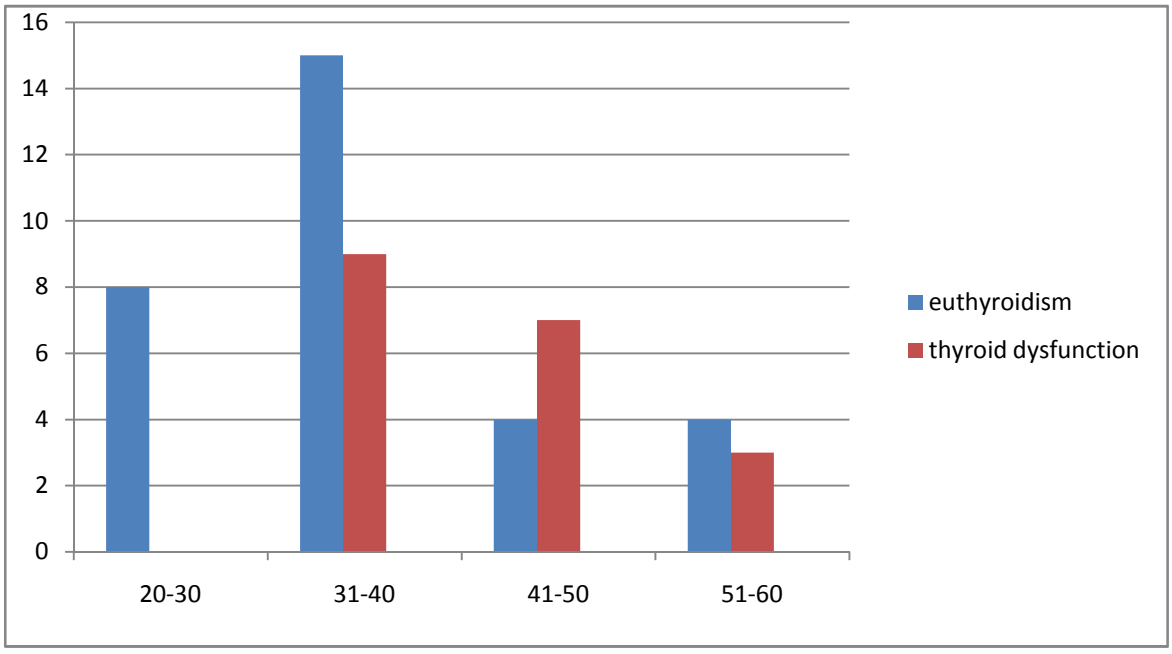

Figure 20 : Association of Age with Thyroid dysfunction

Pearson chi square test value : 8.044

P value 0.045

Significant

Table 20 : Association of Sex with Thyroid dysfunction in HIV patients

Sex	Euthyroidism	Thyroid dysfunction	Total
Male	9	6	15
Female	22	13	35
Total	31	19	50

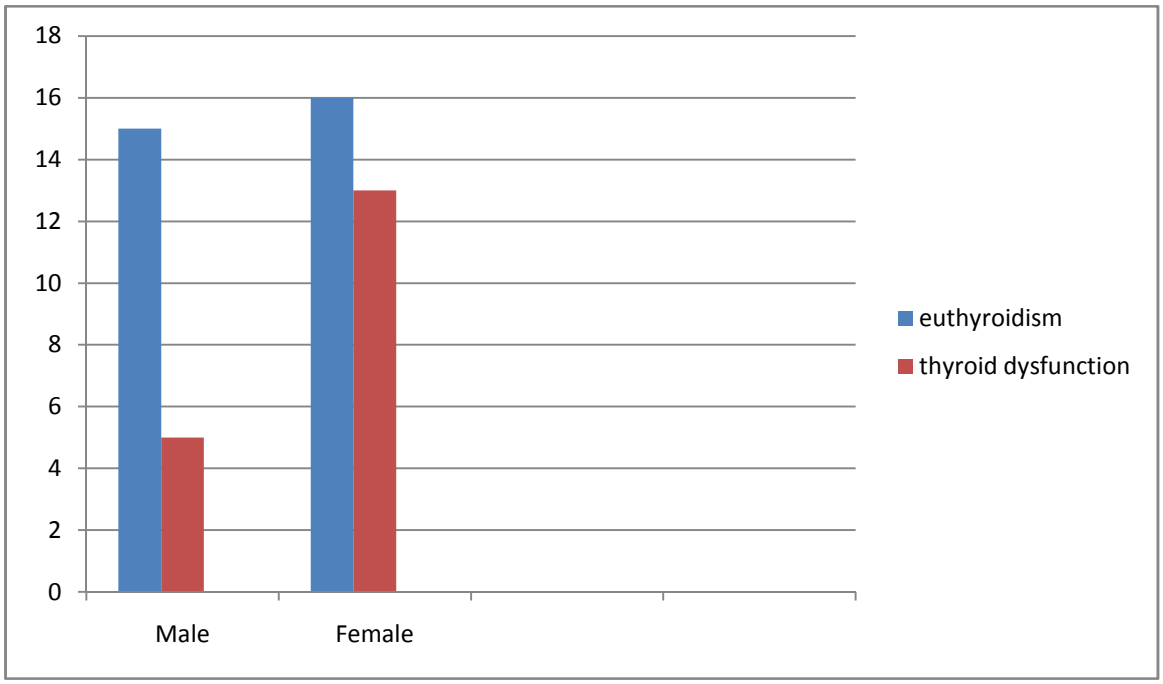

Figure 21: Association of Sex with Thyroid dysfunction in HIV patients

Pearson chi square value 2.391

P value 0.122

Not significant

Table 21 : Association of CD4 Count with Thyroid Dysfunction

CD4 Count	Number of Euthyroid	Number of thyroid dysfunction	Total
<200	8	11	19
200-500	23	8	31
>500	0	0	0
Total	31	19	50

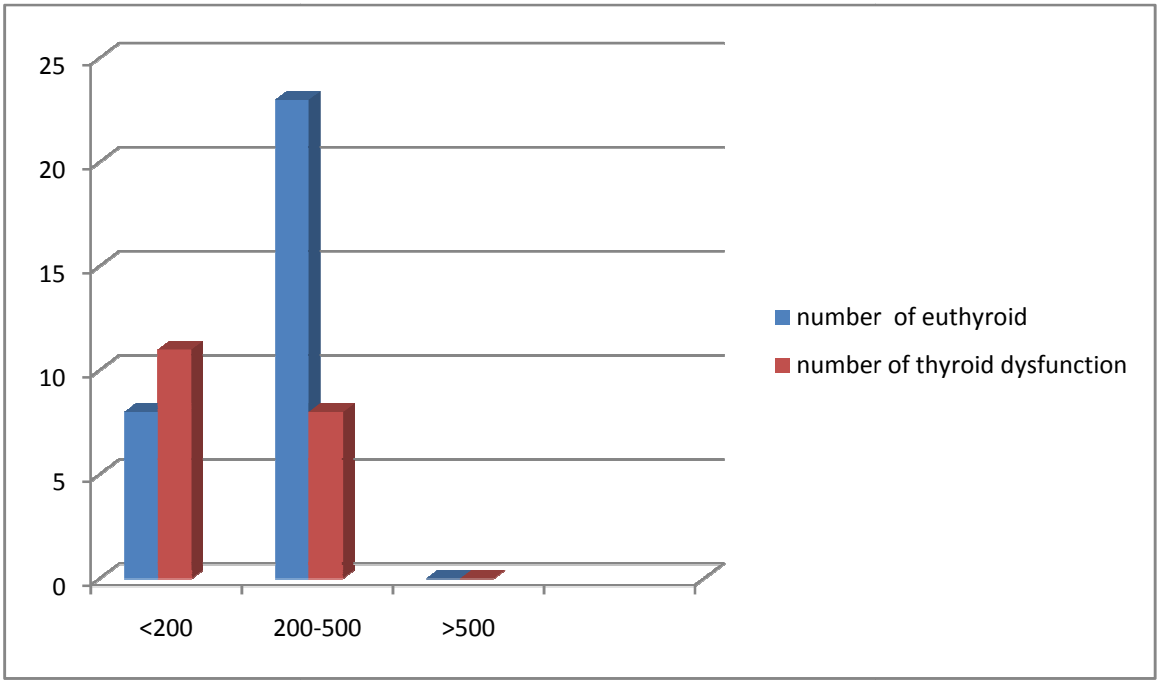

Figure 22 : ASSOCIATION OF CD4 COUNT WITH THYROID DYSFUNCTION

Pearson chi square value 5.148 P value .02 Significant

ODDS RATIO-.253 (CI-.075-.853) Significant

Table 22 : ASSOCIATION OF WHO CLINICAL STAGE AND THYROID DYSFUNCTION

WHO clinical stage	Euthyroid patients	Thyroid dysfunction patients	Total
1	4	0	4
2	14	3	17
3	8	7	15
4	5	9	14
Total	31	19	50

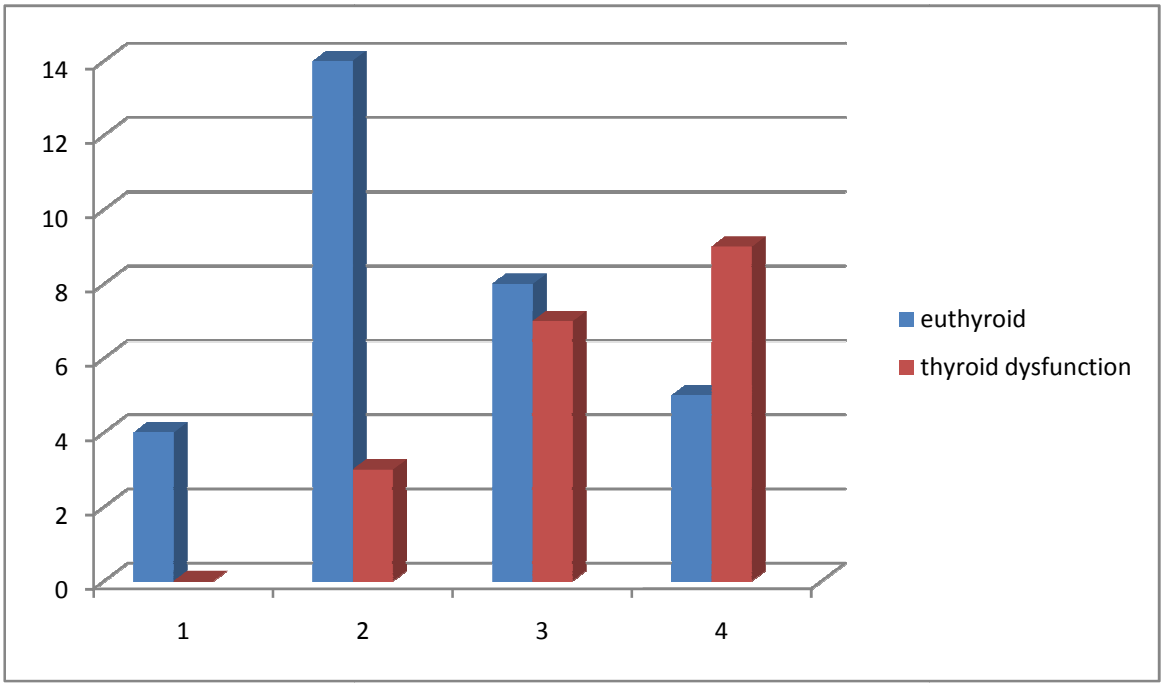

Figure 23 : ASSOCIATION OF WHO CLINICAL STAGE AND THYROID DYSFUNCTION

Pearson chi – square value 10.025

P value 0.018, Significant

Table 23: Association of pallor with thyroid dysfunction

Pallor	Euthyroid	Thyroid dysfunction	Total
Present	11	13	24
Absent	20	6	26
Total	31	19	50

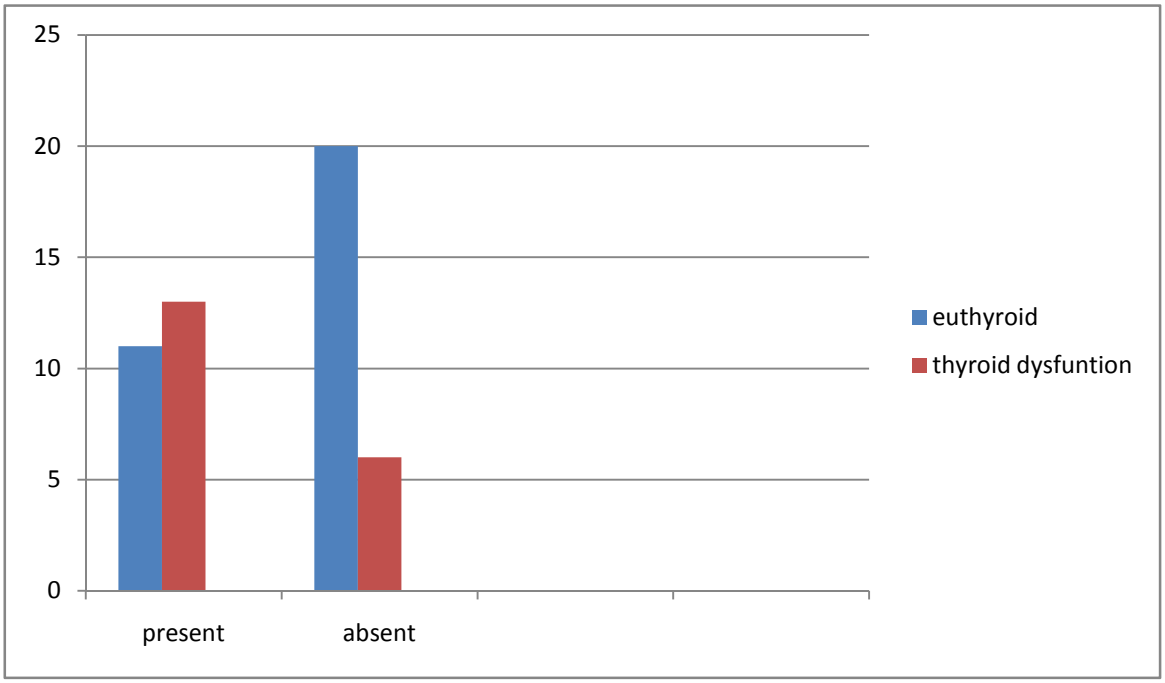

Figure24: Association of pallor with thyroid dysfunction

Pearson chi square value → 5.120 P value → 0.024 Significant

Odds ratio : 0.254 with 95 % CI – 0.075 to 0.856 is statistically significant .

Table 24 : Association of oral candidiasis with thyroid dysfunction

Oral candidiasis	Euthyroidism	Thyroid dysfunction	Total
Present	16 53.3 %	14 46.7 %	30 100 %
Absent	15 75 %	5 25 %	20 100 %
Total	31 62%	19 38 %	50 100%

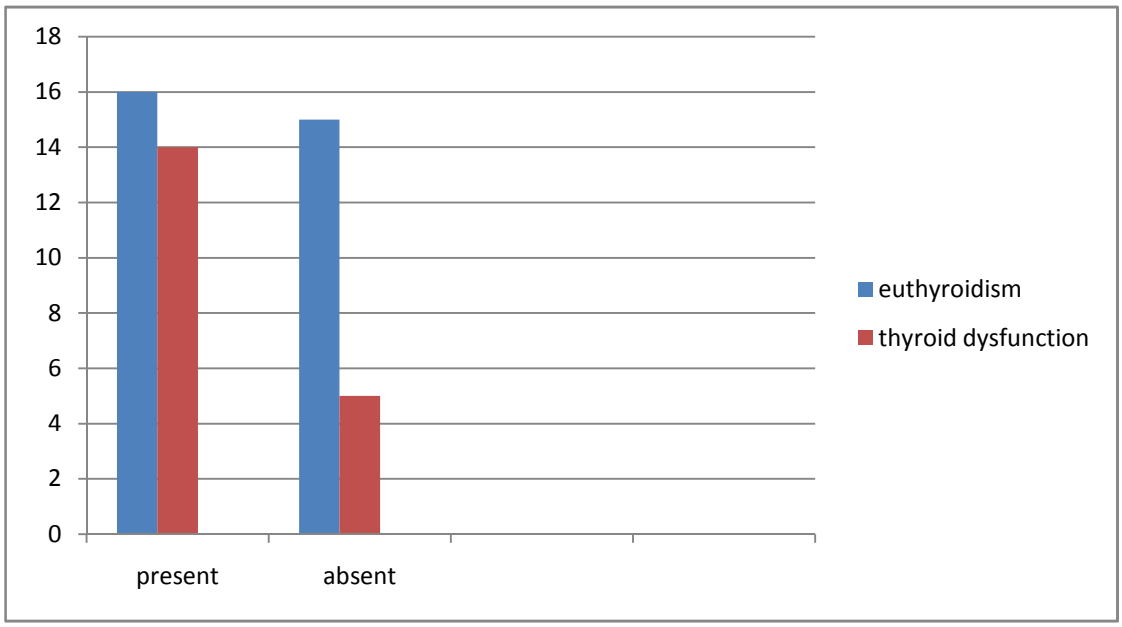

Figure 25 : Association of oral candidiasis with thyroid dysfunction

Pearson chi square value : 2.391 P value : 0.122 Not significant

Odds ratio: 0.381 with CI 0.110 to 1.317 - Not significant

Table 25: Association between Haemoglobin and thyroid dysfunction

Haemoglobin in g/dl	Euthyroid	Thyroid dysfunction	Percentage
<6	0	1	1
6.1-9	3	10	13
9.1-12	17	6	23
12.1 and above	11	2	13
Total	31	19	50

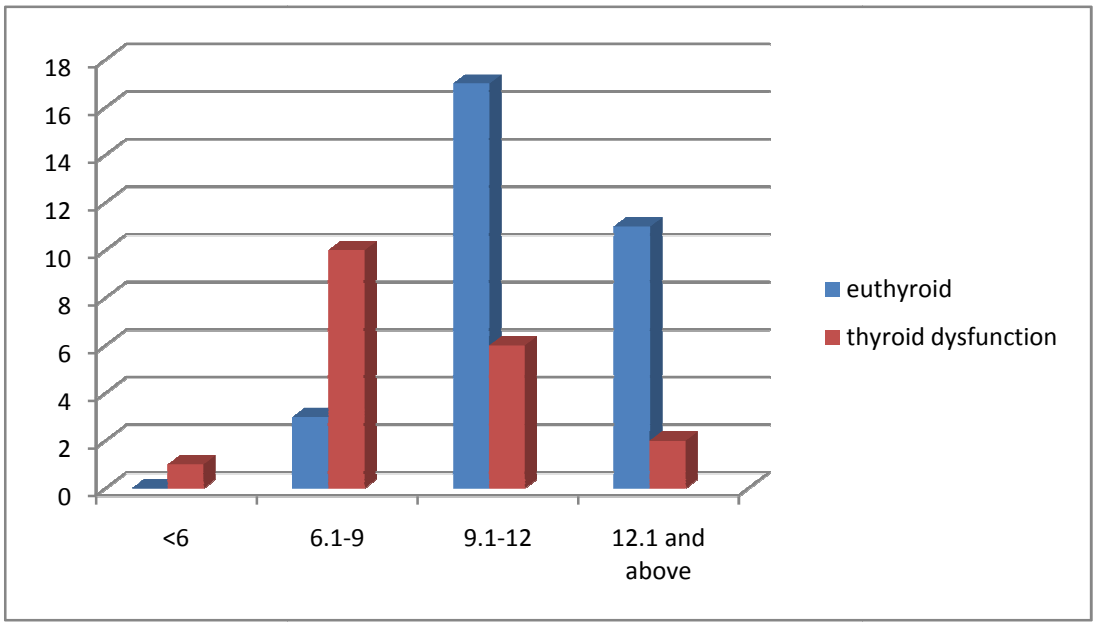

Figure 26 : Association between haemoglobin and thyroid dysfunction

Pearson chi square value 14.199

P value 0.003 Significant

DISCUSSION

The study was conducted in the department of General Medicine, Coimbatore medical college hospital, Coimbatore. Fifty HIV positive symptomatic patients who gave consent to be part of the study were enrolled in the study. All patients were evaluated both clinically and investigation wise as per the pretested proforma.

ASSOCIATION OF AGE OF HIV PATIENTS WITH THYROID DYSFUNCTION

In this study the Mean age was 38.84 ± 16.68 SD . Out of 50 patients in our study 48% were in the age group of 31 to 40 years and 22% were of 41 to 50 years age group and 16 % were of 20 to 30 years and 51 to 60 years age group people constituted 14% . Most of the studies that were refered showed similar age wise distribution.

- The Indian study by Palanisamy et al had a mean age of 49 years.
- The Beltran et al had mean age of 44 years.
- Study by Sundar et al had mean age of 35.81 years
- Madge et al study had mean age of 37 years
- The study by Carter M et al found that hypothyroidism in HIV patients was more in older patients

In our study thyroid dysfunction was most prevalent in 31 to 40 years of age. There was statistically significant association established between Age and Thyroid dysfunction with Pearson chi square test

value : 8.044 P value 0.045, Statistically Significant.

Sex-wise distribution of HIV positive patients :-

In our study of the 50 patients studied 20 were males and 30 were females that is 40% were males and 60 % were females.

- In the **Beltran et al** cohort of 350 subjects,236 were men and 113 were females.[38]
- **Calza et al** studied 202 HIV-infected patients of which 95% were men.[7]
- **Madge et al** studied 1565 HIV positive individuals, of which 1233 were males and 332 were females.56 That is 79 % male and 21 % Most of these studies have a male predominance in their study groups.
- **Bongiovanni et al** studied 190 consecutive HIV positive subjects among which 123 were males and 67 females.[8]

- **Ketsamathi et al** A cross-sectional study was conducted. A total of 200 HIV-infected outpatients were included. 97 patients (48.5%) were male and 103 (51.5%) were female.[63]

Most of these studies had male preponderance in excess.

Table 26 : Comparison of percentage distribution of males and females in different studies

	Palaniswamy pashupathi et al. [72]	Madge S et al[64]	Wilfredo Richard Engel et al.	Present study
Male	100%	79%	76%	40%
Female	Nil	21%	24%	60%

Sex-wise distribution of thyroid dysfunction in HIV positive

In our study of the 50 patients studied, 19 patients had thyroid dysfunction. Of these 5 were males and 14 were females that is 26.32% were males and 73.68 % were females. Thyroid dysfunction was more common in females than male patients. Statistically gender was not

statistically associated with thyroid dysfunction in HIV patients as p value is .122. Thus gender is not associated with thyroid function abnormalities in HIV patients.

Table 27 : Comparison of thyroid dysfunction in male and female HIV patients

Thyroid dysfunction	Meena LP et al	Present study
Male	40.66%	26.32.1%
Female	Nil	73.68%

Category wise distribution of thyroid dysfunction in the 50 HIVindividuals studied:

Among the 50 HIV patients studied, 19 had thyroid dysfunction that is 38 % and 31 were euthyroid. Of these 20 % had subclinical hypothyroidism , 12 % had hypothyroidism , 2 % had hyperthyroidism and 4 % had Low T3 – sick euthyroidism.

In 2003 Carter M et al The study between May & December 2001, included a cohort of 350 patients 16% of patients (n=56) had

hypothyroidism, of whom 2.6% had overt hypothyroidism, 6.6% subclinical hypothyroidism, and 6.8% a low FT4 level.70

In 2003 Beltran et al A cohort of 350 patients with HIV was screened. Overt hypothyroidism, was detected in 2.6 percent of patients.[38]

Subclinical hypothyroidism was detected in an additional 6.6 percent of patients. Low free T4 was found in another 6.8 percent.

In 2006 Ketsamathi et al A cross-sectional study on 200 HIV-infected outpatients was conducted .27 patients (13.5%) had thyroid function decreased. subclinical hypothyroidism 12 whereas five patients had increased thyroid function -subclinical hyperthyroidism .[59]

Table 28 : Comparison of thyroid dysfunction in HIV patients in different studies

	Christopher et al [74]	Collazos et al[73]	Meena LP et al [54]	Present study
Euthyroid	63%	74.5%	59.34%	62%
Thyroid dysfunction	37%	25.5%	40.66%	38%

In our study thyroid dysfunction – 38 % is comparable with the studies by Christopher et al - 37 % . Meena LP et al – 40.66 % . Few previous studies reported lesser number of thyroid dysfunction in HIV patients.

Table 29 : comparison of different types of thyroid function abnormalitites in HIV patients in different studies

	Christopher et al	Meena LP et al	Collazos et al	Present study
Euthyroid	63%	59.34%	74.5%	62%
Hyperthyroid	Nil	nil	1%	2%
Hypothyroid	2%	10.66%	2.5%	12%
Subclinical hypothyroid	35%	30%	1%	20%
Low T3	Nil	nil	17%	4%

In our study hypothyroidism prevalence was 12 % which is comparable to that of Meena et al study was 10.66 %. Euthyroidism was present in 62 % which is comparable to Christopher et al 63%. Even if

the previous studies show different percentage by thyroid dysfunction , total thyroid dysfunction 38% was comparable. And in many studies which includes our study also the combined hypothyroidism and subclinical hypothyroidism is found to be the commonest.

Relationship of absolute CD4 counts with respect to HIV patients with and without thyroid dysfunction:

In our study of 50 HIV individuals, the Mean CD4 count was **234.22 ±101.316.** Among these CD 4 count <200 was found in 19 patients that is 38 % of them and 201 – 500 in 62 %, that is 31 patients. The Mean CD4 ± SD with thyroid dysfunction was found to be 226.16 ±155.9, and 212.06 ±164.32 without thyroid dysfunction. On fischer's exact test the P value was calculated**(0.002)** and seen that **there is a strong relationship between Absolute CD4 count & thyroid dysfunction. Thus there is a very strong correlation between a dropping CD4 count and occurrence of thyroid dysfunction.**

In 2003 Beltran et al reported subclinical hypothyroidism in 6.6% and subclincal hypothyroidism was3.5% was correlated with low CD4 counts in a Spanish population.[38]

In 2006 Madeddu G, et al. Nine out of 23 HIV patients had subclinical hypothyroidism TSH was negatively associated with CD4 (P< 0·001). [74]

In 2009 Jain et al reported that abnormal thyroid hormone levels which correlated with the CD4 counts and the severity of the disease.

In June 2011 Sundar S et al. studied 150 male HIV positive subjects. Out of 50 subjects with CD4 count less than 200/ cu.mm, fifteen patients had subclinical hypothyroidism while 11 patients had overt hypothyroidism. Thus CD4 count has strong inverse correlation with TSH (r=-0.257, p= 0.002).[52]

ASSOCIATION OF CD4 COUNT CATEGORIES AND THYROID DYSFUNCTION

Among the 50 pateints in the study,

- Category A- CD4 count < 200/microlitrewas found in 38 % and
- Category B- CD 4 count 200-500 /microlitre was 62 %.
- Category A – 57.89 % had thyroid dysfunction
- Category B -25% had thyroid dysfunction

Thus with category A the occurrence of thyroid dysfunction is more. That is those with CD4 count lesser than 200 had more thyroid dysfunction

ASSOCIATION OF WHO CLINICAL STAGE WITH THYROID DYSFUNCTION

Out of the 50 patients

- 8 % belonged to WHO clinical stage 1
- 34 % belonged to WHO clinical stage 2
- 30 % to WHO clinical stage 3
- 28 % to WHO stage 4.
- All of the stage 1 patients were euthyroid.
- 17.65 % of stage 2 patients had thyroid dysfunction
- 46.67% of stage 3 patients had thyroid dysfunction
- 64.3 % of stage 4 patients had thyroid dysfunction

Thus our study shows that patients with advanced clinical stages are more prone for thyroid dysfunction. That is opportunistic infections in advanced stages of HIV may be implicated in the pathogenesis of thyroid dysfunction. When this was subjected to chi square test statistical significant association between WHO clinical stage of HIV disease and thyroid dysfunction was obtained.

ASSOCIATION BETWEEN HAEMOGLOBIN LEVELS /PALLOR AND HIV PATIENTS WITH OR WITHOUT THYROID DYSFUNCTION

In our study of 50 HIV patients, Mean Hb in HIV positive patients was found to be 10.706 ± 1.99(g/dl). Mean Hb in patients with thyroid dysfunction was 9.87±2.22(g/dl). Mean Hb in patients without thyroid dysfunction was found to be 10.06±2.08(g/dl). And the correlation had P value of 0.02, which was **statistically significant.**

Association of pallor in HIV patients with thyroid dysfunction when correlated had a Pearson chi square value → 5.120 and P value → 0.024 which is statistically Significant .The odds ratio for the association was found to be 0.254 with 95 % CI – 0.075 to 0.856

In 2008 Mathews SE et al Study on 187 patients and out of them anemia was found in 35.64% of patients in Group A that is on HAART and 45.34% in Group B that without HAART. The prevalence of anemia was significantly more in immunological and clinical AIDS that is 42.05% and 70.58% respectively in contrast to only 28.57% in asymptomatic HIV infection.[71]

- Thus our study shows significant relation between low Hemoglobin and pallor and advanced HIV disease

ASSOCIATION OF ORAL CANDIDIASIS AND THYROID DYSFUNCTION

Table 30 : Oral candidiasis and thyroid dysfunction

Oral candidiasis	Euthyroidism	Thyroid dysfunction	Total
Present	16 53.3 %	14 46.7 %	30 100 %
Absent	15 75 %	5 25 %	20 100 %
Total	31 62%	19 38 %	50 100%

60% of the study population had oral candidiasis and 46.7% of those with oral candidiasis had thyroid dysfunction. Of the 19 patients who had thyroid dysfunction 14 had oral candidiasis. Pearson chi square value for the association was : 2.391 and P value was 0.122 which is not statistically significant. Thus oral candidiasis is not associated with thyroid dysfunction in HIV but may be due to HIV infection per se.

RESULTS COMPILED

- Among the 50 patients studied, mean age was 38.84±8.34 years.
- 20 were males and 30 were females.
- 38 % had abnormal thyroid function test.
- Of those with thyroid dysfunction 40%-males and 60% - females.
- Thyroid dysfunction was more common in female HIV patients.
- No statistical significant relation was present between thyroid dysfunction and gender.
- 62 % were euthyroid and 38 % had thyroid dysfunction of them 20% had subclinical hypothyroidism, 12 % had hypothyroidism, 2% had hyperthyroidism and 4% had sick euthyroidism. Thus subclinical hypothyroidism was the most common thyroid dysfunction in ART naive HIV patients
- 57.89 % of those with thyroid dysfunction had CD4 count <200 / μL p value 0.023.
- 46.67 % of those with thyroid dysfunction were of WHO clinical stage 3 and 64.3 % of stage 4 patients had thyroid dysfunction. Pearson chi – square value 10.025 with p value 0.018 which is significant statistically

- 57.89 % of those with thyroid dysfunction had hemoglobin less than 9 g/dl chi square value – 14.199 and p value- 0.003 statistically significant.
- Oral candidiasis is not associated with thyroid dysfunction with HIV disease.

CONCLUSION

- In our study thyroid dysfunction was most prevalent in 31 to 40 years of age. There is statistically significant association between age and thyroid dysfunction in HIV patients.
- Thyroid dysfunction is more common in female HIV patients in our study but statistically the association of gender with thyroid dysfunction in HIV patients is absent.
- Subclinical hypothyroidism is the most common thyroid dysfunction in HIV patients, with hypothyroidism the next common and low T3- sick euthyroidism the next common .
- Thyroid dysfunction is more common with lower values of CD4 counts .
- Thyroid dysfunction is most common in stage 4 WHO clinical stage of HIV disease and next common in stage 3, thus thyroid dysfunction is more common in advanced HIV disease.
- Hence thyroid function test screening may be done as screening in patients with advanced HIV disease – WHO clinical stage 3 or 4 and low CD4 counts <200 per microlitre.

- Pallor and Haemoglobin<9 g/dl is associated with thyroid dysfunction in HIV patients. Hence HIV disease patients with anaemia may be screened for thyroid dysfunction.
- Thyroid function abnormalities need to be detected earlier even at subclinical level especially before starting ART in patients with advanced HIV disease as ART initiation itself can push the patient with subclinical hypothyroidism to frank hypothyroidism and those with hypothyroidism to severe hypothyroidism leading to increased morbidity.

SUMMARY

Our study is a prospective study of 50 HIV seropositive patients who attended out- patient clinic or was admitted to general medicine wards of Coimbatore medical college hospital , Coimbatore.

- Thyroid function alteration is common in HIV infection and can be detected in early phase of the disease. The thyroid function abnormalities are HIV specific and prevalence is higher than that of the normal general population.

- With advanced thyroid disease the prevalence of thyroid disease is also higher.

- This study is done to find the thyroid dysfunction in HIV positive newly diagnosed patients who are not started on antiretroviral therapy.

- 50 newly diagnosed HIV positive patients who gave consent for the participation in the study were studied, their T3 T4 TSH results were done and it was correlated with their CD4 counts and clinical stage of disease.

- The patients were all evaluated based on the pretested proforma and confidentiality of the information was strictly maintained.

- Patients who are known thyroid disease or already on Thyroxin treatment and patients on drugs altering thyroid function and Patients who had thyroid surgery in the past and pregnant patients and patients on oral contraceptive pills were excluded from the study.
- Statistical analysis of the data so collected was done.
- HIV serology was done by ELISA, CD4 counts by flow cytometry and T3 T4 TSH by electrochemiluminescence method.
- The mean age of the study group was 38.84 ± 8.34 SD .
- There was statistically significant association between age and thyroid dysfunction.
- Our study had 40 % males and 60 % females.
- There was no significant association between gender and thyroid dysfunction in HIV patients.
- Of the 50 patients studied, 38 % had thyroid dysfunction.
- Subclinical hypothyroidism was the most common thyroid dysfunction In HIV patients in our study.

- 57.89 % of those with thyroid dysfunction had CD4 count <200 / µL p value 0.023. 46.67 % of those with thyroid dysfunction were of WHO clinical stage 3 and 64.3 % of stage 4 patients had thyroid dysfunction.

  Pearson chi – square value 10.025 with P value 0.018 which is significant statistically.

- There was statistically relation between CD 4 count and thyroid dysfunction.

- It was found in the study that advanced WHO clinical stage of the disease was associated with more occurrence of thyroid dysfunction. 46.67 % of WHO clinical stage 3 and 64.3 % of stage 4 patients had thyroid dysfunction and chi square value 10.025, p value 0.018.

- Thus in our study thyroid dysfunction was much prevalent in those with advanced HIV disease.

- So if HIV patient has low CD 4 count there is high chance of thyroid dysfunction.

- 57.89 % of those with thyroid dysfunction had hemoglobin less than 9 g/dl chi square value – 14.199 and p value- 0.003 statistically significant.

- Pallor and low haemoglobin is associated with thyroid dysfunction and hence HIV disease patients with anaemia should be screened for thyroid dysfunction.

- Hence thyroid function screening may be done in newly diagnosed HIV patients with –CD4 counts <200 / µL or WHO clinical stage 3 or 4 or if patient has hemoglobin <9 g/dl or pallor.

- Thyroid function abnormalities need to be detected earlier even at subclinical level especially before starting ART in patients with advanced HIV disease as ART initiation itself can make the patient with subclinical hypothyroidism to go in for a frank hypothyroidism and those with hypothyroidism to severe hypothyroidism leading to increased morbidity.

- So based on the findings of our study it is suggested that thyroid function screening be done in HIV patients with WHO clinical stage 3 or 4 or CD 4 count < 200/µl and also those with pallor clinically or Hemoglobin <9 g/dl.

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ANNEXURE

PROFORMA

NAME: AGE:

SEX: Patient ID :

ADDRESS: OCCUPATION:

HISTORY: SYMPTOM PRESENTATION

Chief complaints:

HOPC:

1)Weight loss :yes/no…….duration……..quantity:……

2) Headache, nasal discharge, ear discharge, cough: yes/no

3)ORAL CAVITY:

Splits at angle of the mouth:yes/no…….. Ulcers in mouth:yes/no…….

Oral thrush:-yes/no…….duration……..

3)SKIN:

Painful rash:yes/no…… duration….

Pruritic lesion:yes/no……. Scaly itchy skin

lesions:yes/no…….duration…….

4)Fever:yes/no…….type……..duration……diuranal variation:……

5)Diarrhea/vomiting:yes/no….frequency…quality….quantity: ……..

6)Cough, dyspnoea:yes/no……..type…….variation…….duration…….

7)Painful anogenital / orolabial wound: yes/ no……..duration…….

8)Retrosternal pain/dysphagia : yes/no…….duration……

9)Visual symptoms: Diminished/blurring of vision: yes/no……

10)Headache: yes/no….type….duration... confusion: yes/no……..

Drowsiness: yes/no……..Behavioural change:…….

Muscular weakness: yes/no…… Numbness/tingling: yes/no……

Past history: PTB: yes/no…. h/o:Previous treatment for CA: yes/no…..

h/o CNS infections: yes/no… h/o recurrant oral ulcerations: yes/no…

h/o diarrhea: yes/no…….duration…….frequency……..

Drug history:

Personal history:

Menstrual history:

Bowel/Bladder:normal/altered …….

Specific history(thyroid):

fatigue: irritability: weakness: heat intolerance:constipation: sweating

cold intolerance: palpitations:slowed mentation: tremors:

hoarseness of voice: muscle weakness:

Clinical examination:

BMI:

Thyroid examination:

Slow cerebration: Attention span:

Slow movement : Tremors:

Slowing of ankle jerk: Tachycardia:

Weight gain: Weight loss:

Thyroid local examination:

Eye examination: **Skin examination:**

Nails: **Lymph nodes:**

Oral thrush

Pallor- icterus- cyanosis- clubbing- pedal edema-

Pulse:.. BP… Temperature….- R.R….

CHEST:

Inspection: Shape/symmetry: Trachea- Apical impulse-

Palpation: Chest movements: Chest measurements:

Palpable rhonchi/crackles:

Percussion:

Auscultation: Breath sound Added sounds**:**

CVS: JVP:…… Apical impulse

S1……S2……..S3……S4……. Murmurs:……

Abdomen:

Organomegaly:+/- Free fluid: Mass:

CNS: higher mental functions:

neck stiffness/kernig's: focal deficits:

WHO clinical stage:(2/3/4)-

Investigations:CD4-

Immunological stage:

CBC

ECG

LFT

RFT

Chest x-ray-

THYROID:

T3 …. T4…. TSH….

body fluid analysis(if indicated): **Sputum:** (when indicated)

Stool exam: (when indicated) **Urine microscopy:**

Lymph node fnac/biopsy: (when indicated)

Neuro-imaging(when indicated)

CONSENT FORM

Yourself Mr./Mrs./Ms……..…… are being asked to be a participant in the research study titled **"STUDY OF THYROID FUNCTION ABNORMALITIES IN NEWLY DIAGNOSED HIV PATIENTS"** in CMC Hospital, Coimbatore, conducted by Dr.Dhanya.S.Kumar Post Graduate Student in the Department of General Medicine, Coimbatore Medical College. You satisfy eligibility as per the inclusion criteria. You can ask any question you may have before agreeing to participate.

Research Being Done

"STUDY OF THYROID FUNCTION ABNORMALITIES IN NEWLY DIAGNOSED HIV PATIENTS**"** in Coimbatore Medical College

Purpose of Research

(1) To study thyroid function abnormalities in newly diagnosed HIV patients.

(2) To find out relation between thyroid function abnormalities and severity of illness in HIV infected patients

Procedures involved

The research includes detailed clinical examination including medical history, physical examination. Laboratory investigations including HIV ELISA test , thyroid function tests, complete haemogram, CD4 count.

Decline from Participation

You have the option to decline from participation in the study existing protocol for your condition.

Privacy and Confidentiality

Privacy of individuals will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization to publish Results

Results of the study may be published for scientific purposes and/or presented to scientific groups; however you will not be identified.

Statement of Consent

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me, and I may ask questions at any time.

---------- ----------

Signature /Left thumb impression Date

(Volunteer)

---------- ----------

Signature of witness Date

ஒப்புதல் படிவம்

பெயர் :

பாலினம் : வயது :

முகவரி :

அரசு கோவை மருத்துவக் கல்லூரியில் மகப்பேறு மருத்துவ துறையில் பட்ட பயிலும் மாணவி அவர்கள் மேற்கொள்ளும் "**எச்.ஐ.வி நோயாளிகளில் தைராய்டு பிரச்சனை**" குறித்த ஆய்வில் செய்முறை மற்றும் அனைத்து விவரங்களையும் கேட்டுக் கொண்டு எனது சந்தேகங்களை தெளிவுப்படுத்திக் கொண்டேன் என்பதை தெரிவித்துக் கொள்கிறேன்.

நான் இந்த ஆய்வில் முழு சம்மதத்துடன், சுய சிந்தனையுடனும் கலந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் என்னுடைய அனைத்து விபரங்கள் பாதுகாக்கப்படுவதுடன் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை என்பதை தெரிவித்துக் கொள்கிறேன். எந்த நேரத்தில் இந்த ஆய்விலிருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இடம் : கையொப்பம் / ரேகை

நாள் :

KEY TO MASTER CHART

CONSTITU SYMP – CONSTITUTIONAL SYMPTOMS

SYMP- Symptoms

S/S – Signs and symptoms

BMI - Body Mass Index

LN – lymph node

HB – haemoglobin

CXR- chest X ray

MASTER CHART

sl No:	Patient ID	AGE	SEX	CONSTITU SYMP	SYSTEMIC SYMP	S/S of hypothyroidism	S/S of hyperthyroidism	BMI	GOITRE	PALLOR	LN	ORAL CANDIDIASIS	HB (g/dl)	CXR	T3	T4	TSH	CD4	clinical diagnosis	WHO clinical stage	DIAGNOSIS
1	10231	48	male	present	RS-cough sputum	absent	absent	19	no	yes	no	yes	7.8	PT	54	6.8	9.8	28	TB meningitis	4	hypothyroidism
2	10239	58	female	present	CNS - seizures fever	absent	absent	23	no	no	no	no	11	PT	153	5.6	1.85	200	pulmonary TB	3	euthyroidism
3	10246	33	female	present	RS-cough sputum	absent	absent	22	no	yes	no	yes	9	consolidation	98	6.5	3.7	298	pneumonia / oral candidiasis	3	euthyroidism
4	10694	38	female	absent	nail infection	absent	absent	23.5	no	no	no	yes	11	normal	62	7	17.2	420	r/c oral ulcer/ fungal nail inf	2	subclinical hypothyroidism
5	10693	40	male	present	skin lesion	absent	absent	24	no	no	no	no	12.6	normal	120	7.6	3.6	280	herpes zoster	2	Euthyroidism
6	10687	34	female	present	diarrhoea	absent	absent	19	no	yes	no	no	8.6	normal	128	6.8	4.2	294	Cryptosporidiosis	2	euthyroidism
7	10688	30	female	present	RS-cough sputum	absent	absent	21	no	no	no	no	12	consolidation	134	6.2	2.8	340	Pneumococcal pneumonia	2	euthyroidism
8	10690	40	male	present	RS-cough sputum	absent	absent	20	no	yes	no	yes	10	miliary TB	98	8.2	4.5	200	Miliary TB	3	euthyroidism
9	10264	31	female	absent	oral candidiasis	absent	absent	24	no	yes	no	yes	9.6	normal	104	6.4	3.4	300	oral candidiasis	2	euthyroidism
10	10283	33	female	present	chronic diarrhoea	absent	absent	19	no	yes	no	yes	8	normal	73	5.2	7.8	145	chronic diarrhoea	3	subclinical hypothyroidism
11	10351	48	male	absent	RS-cough sputum	absent	absent	22	no	yes	no	no	9.2	PT	120	5.8	3.2	260	pulmonary TB	3	euthyroidism

12	10347	52	female	present	RS-cough sputum	absent	absent	23	no	no	no	yes	12	PCP pneumonia	68	6.98	3.33	192	PCP pneumonia	4	euthyroidism
13	10339	30	male	absent	skin lesion	absent	absent	22	no	no	no	no	12.6	kaposi sarcoma	142	5.4	3.8	380	kaposi's sarcoma	2	euthyroidism
14	10336	41	female	present	headache	absent	absent	23	no	no	no	no	12	normal	149	7.2	8.6	220	meningitis	3	subclinical hypothyroidism
15	10312	30	male	present	intestinal obstruction	absent	absent	24	no	no	no	yes	12	normal	140	6.7	4.4	264	oral candidiasis	2	euthyroidism
16	10642	32	female	present	oral candidiasis	absent	absent	18	no	no	no	yes	13	normal	40	5.4	3.2	124	pulmonary TB	3	Low T3
17	10650	33	male	absent	absent	absent	absent	24	no	no	yes	no	12	normal	76	7.4	2.4	424	Persistent generalised lymphadeopathy	1	euthyroidism
18	10659	52	female	absent	absent	present	absent	28	no	yes	no	yes	12	normal	50	8.87	8.9	350	herpes zoster	2	hypothyroidism
19	10666	40	male	absent	CNS-altered sensorium	absent	absent	24	no	no	no	yes	12	normal	110	7.6	3.6	180	PMLE	3	euthyroidism
20	10680	48	female	present	abdominal pain	absent	absent	20	no	no	no	yes	12	normal	132	7.2	2.2	120	Abdominal TB	4	euthyroidism
21	10377	42	female	absent	abdominal pain	absent	present	22	no	no	no	yes	13	normal	176	15	0.3	212	oral candidiasis	2	hyperthyroidism
22	10370	38	female	absent	recurrent oral ulceration	absent	absent	23	no	no	no	yes	12.4	normal	140	8.2	3.6	232	oral candidiasis / rec oral ulceration	2	euthyroidism
23	10364	30	male	present	RS-cough sputum	absent	absent	22	no	yes	no	yes	10	bronchopneumonia	122	7.4	2.6	280	pneumococal pneumonia /candidiasis	2	euthyroidism

24	10359	33	female	present	dysphagia	absent	absent	17	no	yes	no	yes	7.4	normal	40	5.4	2.8	64	esophageal candidiasis	4	Low T3
25	10353	31	male	present	RS- cough sputum	absent	absent	24	no	no	no	no	11	b/l pneumonia	130	8.7	8.3	360	b/l staph pneumonia	3	subclinical hypothyroidism
26	10603	28	female	present	RS- cough sputum	absent	absent	18.6	no	yes	no	no	10.2	PT	134	8	4.2	288	pulmonary TB	3	euthyroidism
27	10606	29	female	present	oral candidiasis	absent	absent	22	no	no	no	yes	13	normal	126	7.6	3.2	280	oropharyngeal candidiasis	2	euthyroidism
28	10607	30	female	present	RS- cough sputum	absent	absent	20	no	no	no	yes	10	consolidation	120	7.8	3	280	Pneumococcal pneumonia	2	euthyroidism
29	10633	42	male	present	cough	absent	absent	20	no	yes	no	yes	9	PCP pneumonia	72	5.6	6.2	94	PCP pneumonia	4	subclinical hypothyroidism
30	10623	38	female	present	CNS- headache	absent	absent	22	no	yes	no	yes	10.2	normal	154	6.7	3.6	132	meningitis	3	euthyroidism
31	10410	39	male	present	nil	absent	absent	22	no	yes	no	yes	8.8	normal	142	5.8	3.33	360	oral candidiasis	2	euthyroidism
32	10404	56	female	present	cough and neck swelling	absent	absent	18	no	yes	yes	yes	6	PT	50	6.2	9.4	85	Disseminated tuberculosis	4	hypothyroidism
33	10409	30	female	absent	oral candidiasis	absent	absent	22	no	no	no	yes	13	normal	122	8	2.8	320	oropharyngeal candidiasis	2	Euthyroidism
34	10392	36	male	absent	RS- cough sputum	absent	absent	19	no	yes	no	yes	9.6	PT	150	7.2	4.4	220	pulmonary TB	3	euthyroidism
35	10383	32	female	absent	head ache eye pain	absent	absent	21	no	yes	yes	yes	9	normal	99	6.5	8	99	CMV retinitis	4	subclinical hypothyroidism
36	10515	42	male	absent	skin lesion	absent	absent	23.5	no	no	no	no	13	normal	88	7.2	4.2	304	seborrheic dermatitis	2	euthyroidism
37	10519	34	female	absent	absent	absent	absent	22.5	no	no	no	no	12	normal	110	7.6	3.6	388	asymptomatic	1	euthyroidism
38	10536	38	male	present	cough	absent	absent	21	no	yes	no	no	8.5	PT	52	6.7	8.9	300	pulmonary TB	3	hypothyroidism

39	10593	46	male	absent	severe weight loss	absent	absent	18	no	yes	no	no	7.8	normal	154	7.2	9	320	severe weight loss	3	subclinical hypothyroidism
40	10597	51	female	absent	CNS - altered sensorium	absent	absent	24	no	yes	no	no	9	normal	69	7.2	8	280	HIV encephalopathy	4	subclinical hypothyroidism
41	10511	58	male	present	CNS- headache/ seisure	absent	absent	21	no	yes	yes	no	9.2	normal	64	5.6	4	88	CNS Toxoplasmosis	4	euthyroidism
42	10476	35	female	present	skin lesion	absent	absent	23	no	no	no	no	14	normal	110	6.4	4	212	herpes zoster	2	euthyroidism
43	10465	44	female	present	nephropathy	absent	absent	23	no	yes	no	yes	8	cardiomegaly	94	7.3	7.3	138	HIV associated nephropathy	4	subclinical hypothyroidism
44	10458	31	female	present	CNS headache LOC	absent	absent	24	no	no	no	yes	12	normal	42	11.3	43.86	90	CNS Toxoplasmosis	4	hypothyroidism
45	10448	52	male	absent	absent	absent	absent	24	no	no	no	no	14	normal	140	6.9	4.2	276	asymptomatic	1	euthyroidism
46	10447	34	female	present	absent	absent	absent	22	no	no	yes	no	13.2	normal	132	8.2	4	340	Persistent generalised lymphadeopathy	1	euthyroidism
47	10443	32	female	present	cough sputum	absent	absent	22	no	yes	no	yes	9.2	PCP pneumonia	42	3.4	10	186	PCP pneumonia	4	Hypothyroidism
48	10438	45	male	present	headache /seizure	absent	absent	21	no	no	no	yes	12.4	normal	48.5	10	3.6	104	TB meningitis	4	euthyroidism
49	10424	43	female	present	RS- cough sputum	absent	absent	20	no	yes	no	yes	8.8	PT	69	9.4	6.8	120	pulmonary TB	3	subclinical hypothyroidism
50	10421	32	male	present	RS- cough sputum	absent	absent	23	no	no	no	no	13.2	consolidation	100	8.4	3.8	240	bacterial pneumonia	4	euthyroidism